Performance of the faecal immunochemical test for the detection of colorectal neoplasms and the role of proton pump inhibitors in their diagnostic accuracy

Subashini Chandrapalan1,2 | Siew Wan Hee1 | Monika M. Widlak1,2 | Alexia Farrugia1,2 | Mohammed T. Alam3 | Steve Smith4 | Ramesh P. Arasaradnam1,2,5,6

Abstract

Aim: The faecal immunochemical test (FIT) is currently utilized in both symptomatic and screening populations, but little is known about factors that affect its performance. For example, proton pump inhibitor (PPI) therapy has been purported to increase false negative rates. This has significant implications given the extent of PPI prescriptions. The aim of this work was to evaluate the performance of the FIT for the detection of colorectal neoplasms and the impact of PPI therapy on its diagnostic accuracy.

Method: Symptomatic patients referred on the suspected cancer pathway and those on polyp surveillance between 2015 and 2019 were approached to participate. Estimates of the accuracy of FIT at different cut-off levels in diagnosing colorectal neoplasms were made. Logistic regression was used to assess the effect of PPIs on the FIT results.

Results: A total of 667 participants were eligible for the final analysis. At a cut-off of 10 μg/g faeces, the overall sensitivity and specificity of FIT for the detection of colorectal cancer (CRC) was 0.85 (95% CI 0.71–0.94) and 0.81 (95% CI 0.78–0.84), respectively. For the detection of advanced neoplasia, the sensitivity was 0.70 (95% CI 0.58–0.79) and the specificity was 0.83 (95% CI 0.80–0.86). At higher thresholds, the sensitivity steadily declined whilst specificity increased. PPI therapy did not have a significant effect on the performance of the FIT.

Conclusion: FIT is a good rule-out test for the detection of CRC and advanced neoplasia at lower thresholds. PPI therapy does not appear to have an effect on its diagnostic performance.

KEYWORDS
adenoma, faecal immunochemical test, proton pump inhibitors

INTRODUCTION

The adenoma–cancer sequence is a widely known model in the development of colorectal cancer (CRC) and the mutations at different stages can result in tumour initiation, expansion and invasion [1–4]. The faecal immunochemical test (FIT) has shown promise as a diagnostic test for the detection of CRC. A recent meta-analysis showed that the overall sensitivity and specificity of the FIT (cut-off range of 10–40 μg/g faeces) for the detection of CRC in a symptomatic group was 0.90 and 0.88, respectively [5].
The prevalence of adenoma under the age of 50 years ranges from 15% to 30% [6], while for the over 70s it is as high as 39% [7]. Performance of the FIT for the detection of high-risk adenomas varies across studies depending on the cut-off value applied [8–10]. Amongst these, a larger UK-based study by Cross et al. [10] showed that FIT had a sensitivity of 56.6% and a specificity of 73.7% in post-polypectomy patients with intermediate risk (with three to four adenomas <10 mm or at least one ≥10 mm).

Evidence suggests that only half of the population who undergo colonoscopy following a positive screening test is found to have advanced neoplasia at endoscopic examination [11]. Several studies have attempted to evaluate various factors which could potentially confound the performance of the FIT [gastrointestinal (GI) symptoms, comorbidities, medications, demographics and lifestyle] [12–17]. Amongst these, proton pump inhibitors (PPIs) have recently been the subject of detailed consideration. PPIs are prescribed not only as a treatment for peptic ulcer disease but also as a preventive medication against upper GI bleeding. Growing evidence suggests that PPI use has increased over time, and perhaps has continued over the long term [18–26]. Most of the long-term users of PPIs were aged over 50 years [27,28].

Rodriguez-Alonso [17] et al. found that PPIs were independently associated with lower FIT levels, even after adjusting for age, gender, smoking status, dyslipidaemia, diabetes and nonsteroidal anti-inflammatory drug and antiplatelet use. Several hypothetical mechanisms have been proposed for PPIs and their influence on FIT results. Firstly, PPI therapy suppresses gastric acid secretion and consequently promotes overgrowth of intestinal microbiota [29–33]. This can lead to increased globin degradation. Secondly, PPI therapy inhibits pancreatic secretions, which in turn impairs degradation of globin by pepsin and trypsin [34]. Hence, upper GI bleeding can result in intact globin molecules reaching the lower GI tract, which can be detected by the FIT.

In light of these facts, we set out to investigate the performance of the FIT for the detection of colonic neoplastic lesions as well as the effect of PPI therapy on FIT levels. To our knowledge, this is the first UK study to evaluate the effect of PPIs on the diagnostic performance of the FIT. It extends from our previous study [8] reported in 2017 which was the first study in England in those with lower GI symptoms.

**METHOD**

**Study design and participants**

This is a prospective analysis of quantitative FITs in patients who have had colonoscopy on the suspected cancer referral pathway (also known as 2-week-wait referral) [35] criteria or on the polyp surveillance programme, as per the National Institute for Health and Care Excellence (NICE) guidance, between 2015 and 2019.

The criteria for referrals on the urgent cancer pathway for lower GI cancers are as follows:

- aged 40 and over with unexplained weight loss and abdominal pain or
- aged 50 and over with unexplained rectal bleeding or
- aged 60 and over with iron deficiency anaemia or change in bowel habit or tests showing blood in the faeces.

The detailed referral criteria are available on the NICE website [35].

Ethical approval was granted by the Coventry and Warwickshire Research Ethics Committee, UK, as part of the FAMISHED (Food and Fermentation using Metagenomics in Health and Disease) multicentre study (09/H1211/38) and by the London–Bromley Research Ethics Committee, UK, as part of the FAST (FIT in Adenoma Surveillance study) multicentre study (19/LO/1614).

A total of 1732 participants (1613 urgent symptomatic referrals and 119 patients from the polyp surveillance programme) were approached (Figure 1). Of those, 1065 (61%) participants were excluded for one or more of the following reasons: the consent form was not fully completed, unfit for colonoscopy and bowel preparation, other illness, failure to provide stool sample, insufficient or old FIT sample returned, failure to have the colonoscopy procedure or incomplete colonoscopy.

Patients were considered as exposed to PPIs if they had been taking any form of PPI (omeprazole, lansoprazole, rabeprazole or pantoprazole) within 90 days prior to their FIT and continued to be on a PPI at the time of the FIT. Iron deficiency anaemia (IDA) was defined according to the NICE criteria – for men, haemoglobin (Hb) below 130 g/l and for nonpregnant women Hb below 120 g/l, with confirmed low iron stores. Antiplatelet therapy included clopidogrel, ticagrelor, prasugrel, dipyridamole etc. and anticoagulation therapy included both warfarin and direct oral anticoagulants.

**Intervention and data collection**

All of the study participants had a FIT within 4 weeks prior to their colonoscopy procedure (HM-JACKarc System, Hitachi Chemical Diagnostics Ltd, supplied by Alpha Laboratories Ltd, Eastleigh, UK). Written and pictorial instructions for sample collection were also provided. Demographic details and an exhaustive medical history, focusing on medication, were also obtained either during the face-to-face consultation or over the telephone. The respective general practitioners’ records were cross-checked for accuracy. A quantitative
FIT analysis was performed at the HM-JACKarc analyser at the Midlands and North West Bowel Cancer Screening Hub, Rugby, UK, an ISO15189 accredited laboratory. This method has a limit of detection of 2 µg/g faeces and a limit of quantification of 7 µg/g faeces.

All the colonoscopy examinations were performed by competent endoscopists within a unit accredited to the Joint Advisory Group on Gastrointestinal Endoscopy (JAG). A colonoscopy was considered as complete if caecal intubation was confirmed by identifying the appendicular orifice, ileocaecal valve and triradiate caecal folds, in accordance with the JAG criteria.

Histology reports were reviewed for histological classification of polyps. The number of polyps, their size and their location within the colon were also recorded. Diagnosis from histology reports was classified as normal, invasive carcinoma, adenoma or other bowel condition (inflammatory bowel disease, diverticulosis, microscopic colitis, etc.). A polyp was considered as advanced adenoma if it was ≥10 mm in size or had high-grade neoplasia (HGD) regardless of its villous component (in line with the British Society of Gastroenterology guidelines on post-polypectomy and post-CRC resection surveillance) [36]. Advanced neoplasia was defined if the polyps showed either advanced adenoma or invasive carcinoma.

**Statistical analysis**

Participants’ characteristics were summarized as mean and standard deviation, median and interquartile range (IQR) (continuous variables) and frequency and percentage (categorical variables). A receiver operating characteristic (ROC) curve [37] was plotted to describe the accuracy of the FIT. The sensitivity, specificity, positive predictive value and negative predictive value of the FIT for the detection of CRC, advanced neoplasia and all adenomas were evaluated according to PPI exposure. The 95% CI for sensitivity and specificity were estimated using the method recommended by Zhou et al. [38] and the 95% CI for positive predictive value and negative predictive value were estimated using the method of Mercaldo et al. [39] because some of the estimated proportions were near 0 or 1. Performance of the FIT was evaluated at cut-off levels of 7, 10, 80, 100, 120 and 200 µg/g faeces. Cut-off levels of 80 µg/g faeces and 120 µg/g faeces were selected, as these are the thresholds used in the Scottish and English bowel cancer screening programmes, respectively. A cut-off of 10 µg/g faeces was selected from the national recommendation of FIT thresholds for symptomatic patients and a cut-off level of 100 µg/g faeces was considered from recent NHS England guidance for urgent colorectal investigations under the current COVID-19 pandemic [40]. Further threshold levels of 7 and 200 µg/g faeces were also explored in the light of emerging variable guidance by cancer alliance pathways utilizing different cut-offs in the COVID era. The outcome variables were analysed under three categories: CRC versus all adenoma/other bowel conditions/normal; advanced neoplasia versus nonadvanced adenoma/other bowel conditions/normal; CRC/all adenoma versus other bowel conditions/normal. Fisher’s exact test was used to evaluate the statistical significance of differences between the precision estimates of those who were exposed and not exposed to PPI.

The main and interaction effects of FIT and PPI exposure on the diagnosis of CRC versus all adenoma/other bowel conditions/normal, advanced neoplasia versus nonadvanced adenoma/other

![Study flow diagram of total patients approached and those recruited having met the inclusion criteria](image-url)

**FIGURE 1** Study flow diagram of total patients approached and those recruited having met the inclusion criteria.
bowl conditions/normal and CRC/all adenoma versus other bowel conditions/normal were further investigated with multiple logistic regression adjusted by sex, age and IDA. All statistical analyses were performed using the program R [41].

RESULTS

Basic characteristics of the study population

A total of 667 participants were eligible per protocol to be included in this study. There were 224 (33.58%) participants exposed to PPI with a median age of 70 years (IQR 60–77 years); the 443 (66.42%) participants in the non-PPI group had a median age of 67 years (IQR 56–74 years) (Table 1). The ratio of men to women was about 1:1 and was similar in both PPI exposure groups. Among the 667 participants, 35 (5.25%) were diagnosed with CRC on their colonoscopy examination, 139 (21.99%) had an adenoma and 35 (5.54%) had advanced adenoma. Thus, 70 (10.49%) had advanced neoplasia. A total of 211 (31.63%) were found to have other pathologies, such as inflammatory bowel disease, microscopic colitis and diverticulosis. The colonoscopy was completely normal in 282 (42.28%) participants. The median FIT value was 1.8 µg/g faeces (IQR 0.90–7.40 µg/g) and this was similar in participants who were and were not exposed to PPI. Basic characteristics, concomitant medication, the presence of IDA and the endoscopic findings of the study population, according to their PPI use, are summarized in Table 1.

The performance of the FIT at different cut-off levels

Table 2 presents the precision estimates for the detection of CRC and advanced neoplasia at different FIT cut-off levels according to PPI exposure. At a cut-off of 10 µg/g faeces, the overall sensitivity and specificity in the detection of CRC were 0.86 (95% CI 0.71–0.94) and 0.82 (95% CI 0.78–0.85), respectively. Although the negative predictive value was high, at 0.99 (95% CI 0.98–0.996), the positive predictive value was only at 0.21 (95% CI 0.17–0.24). For those who were not exposed to a PPI, the FIT exhibited a sensitivity of 0.90 (95% CI 0.75–0.97), a specificity of 0.83 (95% CI 0.79–0.86), a positive predictive value of 0.27 (95% CI 0.23–0.32) and a negative predictive value of 0.99 (95% CI 0.97–0.997) for the

| Characteristics                              | Not exposed to PPI (n = 443) | Exposed to PPI (n = 224) | All patients (n = 667) |
|---------------------------------------------|-------------------------------|--------------------------|------------------------|
| Number of patients                          | 442                           | 224                      | 5666                   |
| Age (years)                                 |                               |                          |                        |
| Mean (SD)                                   | 65.30 (12.57)                 | 68.70 (11.22)            | 66.44 (12.23)          |
| Median (IQR)                                | 67 (56–74)                    | 70 (60–77)               | 68 (57–75)             |
| Sex                                         |                               |                          |                        |
| Female, n (%)                               | 216 (48.76)                   | 120 (53.57)              | 336 (50.37)            |
| Male, n (%)                                 | 227 (51.24)                   | 104 (46.43)              | 331 (49.63)            |
| Presence of IDA, n (%)                      | 71 (16.06)                    | 52 (23.21)               | 123 (18.47)            |
| Concurrent medication                       |                               |                          |                        |
| NSAID therapy, n (%)                        | 36 (8.13)                     | 27 (12.05)               | 63 (9.45)              |
| Antiplatelet therapy, n (%)                 | 46 (10.38)                    | 45 (20.09)               | 91 (13.64)             |
| Anticoagulation therapy, n (%)              | 21 (4.74)                     | 20 (8.93)                | 41 (6.15)              |
| FIT value (µg/g faeces)                     |                               |                          |                        |
| Mean (SD)                                   | 79.62 (238.74)                | 38.07 (149.74)           | 65.66 (213.82)         |
| Median (IQR)                                | 1.8 (0.90–7.10)               | 1.80 (0.90–8.17)         | 1.8 (0.90–7.40)        |
| Site of the lesion (right), n (%)           | 354 (79.91)                   | 186 (83.04)              | 540 (80.96)            |
| Histology (colonoscopy results)             |                               |                          |                        |
| Colorectal cancer, n (%)                    | 30 (6.77)                     | 5 (2.33)                 | 35 (5.25)              |
| All adenoma, n (%)                          | 89 (20.09)                    | 50 (22.32)               | 139 (20.84)            |
| Advanced adenoma, n (%)                     | 21 (4.74)                     | 14 (6.25)                | 35 (5.25)              |
| Other bowel conditions, n (%)               | 135 (30.47)                   | 76 (33.93)               | 211 (31.63)            |
| Normal, n (%)                               | 189 (42.66)                   | 93 (41.52)               | 282 (42.28)            |
| Advanced neoplasia\(^a\), n (%)             | 51 (11.51)                    | 19 (8.48)                | 70 (10.49)             |

Abbreviations: FIT, faecal immunochemical test; IDA, iron deficiency anaemia; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs.

\(^a\)Polyps were either advanced adenoma or colorectal cancer.

TABLE 1 Demographics and baseline characteristics of all participants and by proton pump inhibitor (PPI) exposure
detection of CRC. In the PPI group, at the same threshold (10 μg/g faeces), the FIT had a sensitivity and specificity of 0.60 (95% CI 0.21–0.91) and 0.80 (95% CI 0.74–0.85), respectively, and positive and negative predictive values of 0.06 (95% CI 0.03–0.13) and 0.99 (95% CI 0.97–0.996), respectively. There was no statistically significant difference between the precision estimates of both groups.

Figure 2 shows the ROC with its 95% confidence band for detecting CRC from all adenoma, other bowel disease and normal. The area under the curve was 0.90 (95% CI 0.84–0.96). As expected, for the detection of CRC, sensitivity decreases whilst specificity increases at higher FIT threshold levels. The cut-off level of 89.5 μg/g faeces corresponds to the highest sensitivity and specificity (0.80 and 0.93, respectively) for the detection of CRC.

The overall diagnostic performance of the FIT for the detection of advanced neoplasia at a cut-off of 10 μg/g faeces was: sensitivity 0.70 (95% CI 0.59–0.80), specificity 0.84 (95% CI 0.81–0.87), positive predictive value 0.34 (95% CI 0.28–0.39) and negative predictive value 0.96 (95% CI 0.94–0.97). Again, no significant difference in the precision estimates was noted between those who were exposed and not exposed to PPI. The area under the ROC curve was 0.83 (95% CI 0.77–0.88), slightly lower than for the detection of CRC alone (Figure 3). The optimum threshold of FIT to give a best detection rate (sensitivity and specificity of 0.78) for advanced neoplasia corresponds to a cut-off level of 5.65 μg/g faeces.

When CRC and adenoma were pooled together, the FIT showed lower precision estimates with a steady decline in sensitivity at increasing thresholds (Table S1 in the Supporting Information, Figure S1).

The impact of PPI exposure on performance of the FIT in the detection of colorectal neoplasms

Table 3 presents the estimated coefficients of the multiple logistic regression analysis for the detection of CRC and advanced neoplasia from other conditions. Exposure to PPIs did not have any effect on the diagnosis of CRC from all adenoma/other bowel conditions/normal either as a main effect or through its interaction with FIT values. Similarly, PPI exposure did not have any effect on the diagnosis of advanced neoplasia from nonadvanced adenoma/other bowel condition/normal. Table S2 presents the estimated multiple logistic regression for the detection of CRC/all adenoma from other bowel conditions/normal.

DISCUSSION

In this study, we assessed performance of the FIT at different thresholds for the detection of colonic neoplasms as well as the impact of PPI exposure on its diagnostic accuracy. The study population consisted of both symptomatic and asymptomatic (polyp surveillance) groups in order to resemble a general population at average risk with regards to the prevalence of colorectal neoplasms.

The FIT showed better precision estimates for the detection of CRC and advanced neoplasia compared with the rest of the study population (all adenoma, other bowel conditions or normal). At higher thresholds there was a steady decline in its sensitivity whilst it become more specific. These findings are in line with previously published data [10,42].

The prevalence of CRC in the general population is around 0.4% (95% CI 0.3%–0.5%), and for advanced adenoma it is 4.6% (95% CI 3.8%–5.5%) [43]. In this setting, an effective rule-out test should have a high negative predictive value. Although it is a trade-off between sensitivity and specificity, retaining a high specificity increases the power of the test. In our study, for the detection of both CRC and advanced neoplasia, the FIT exhibited better sensitivities at cut-off levels below 100 μg/g faeces whilst maintaining high negative predictive values across various threshold levels (as suggested by NHS England for symptomatic patients under the current pandemic) [40]. Interestingly, the specificity of the FIT does not rapidly decrease when the thresholds are lowered. Hence, choosing a threshold with high sensitivity and a reasonably high specificity (power) would warrant use of the FIT as a good rule-out test, since the prevalence of the conditions is rather low in a population at average risk.

Although PPI exposure resulted in low precision estimates for the FIT, it did not reach a statistically significant level in predicting the outcome – whether CRC from other conditions (all adenoma, other bowel conditions or normal) or advanced neoplasia from other conditions (nonadvanced adenoma, other bowel conditions or normal). A previous study by Rodriguez-Alonso et al. [17] looked at the effect of PPI therapy on performance of the FIT for the detection of CRC and advanced neoplasia. This study showed there was no significant difference between the precision estimates in PPI and non-PPI groups for the detection of CRC, which was similar to our findings. However, there was a statistically significant difference between the two groups for the detection of advanced neoplasia and PPI therapy was associated with false positive and false negative results. Our study findings differed in this regard. Possible explanations are as follows. Firstly, the study population in the above-mentioned Spanish cohort consisted of only symptomatic patients, whereas our study included both symptomatic and asymptomatic (polyp surveillance) patients resulting in a prevalence of 5.25%. Secondly, in the study by Rodriguez-Alonso et al. [17] logistic regression was performed for the false positive and false negative results at a cut-off level of 20 μg/g faeces. Since false positive and false negative rates are dependent on the cut-off value applied, the findings cannot be generalized to other cut-off levels. In our study, the multiple logistic regression model included all faecal immunochemical values, regardless of their cut-off levels, for the detection of colonic neoplasms. Thirdly, the non-PPI group in the aforementioned study largely consisted of patients with normal colonoscopy (normal versus other bowel conditions, 600 (59.8%) vs. 101 (10.1%)) while our non-PPI group had equal proportion of participants with normal and
TABLE 2  Diagnostic accuracy of the faecal immunochemical test (FIT) at various threshold and its 95% confidence interval in the detection of colorectal cancer and advanced neoplasia by proton pump inhibitor (PPI) exposure

| Condition                                      | FIT threshold (µg/g faeces) | Without PPI exposure | PPV          | NPV           | With PPI exposure |
|------------------------------------------------|----------------------------|----------------------|--------------|---------------|------------------|
| Colorectal cancer vs. all adenoma/other bowel conditions/normal | 7                          | 28/330               | 0.93 (0.79–0.98) | 0.79 (0.75–0.83) | 0.26 (0.21–0.29) | 0.99 (0.97–0.99) |
|                                                 | 10                         | 27/341               | 0.90 (0.75–0.97) | 0.82 (0.78–0.85) | 0.27 (0.22–0.32) | 0.99 (0.97–0.99) |
|                                                 | 80                         | 25/380               | 0.83 (0.67–0.93)  | 0.92 (0.89–0.94) | 0.43 (0.34–0.52) | 0.98 (0.97–0.99) |
|                                                 | 100                        | 24/384               | 0.80 (0.63–0.91)  | 0.92 (0.90–0.95) | 0.45 (0.35–0.55) | 0.98 (0.96–0.99) |
| Advanced neoplasia vs. nonadvanced adenoma/other bowel conditions/normal | 7                          | 41/322               | 0.80 (0.67–0.89)  | 0.82 (0.78–0.85) | 0.36 (0.31–0.42) | 0.96 (0.94–0.97) |
|                                                 | 10                         | 39/332               | 0.76 (0.63–0.86)  | 0.84 (0.80–0.88) | 0.39 (0.32–0.46) | 0.96 (0.94–0.97) |
|                                                 | 80                         | 34/368               | 0.66 (0.53–0.78)  | 0.93 (0.91–0.95) | 0.58 (0.47–0.68) | 0.95 (0.93–0.96) |
|                                                 | 100                        | 31/370               | 0.60 (0.47–0.73)  | 0.94 (0.91–0.96) | 0.58 (0.47–0.69) | 0.94 (0.92–0.96) |
|                                                 | 120                        | 28/373               | 0.54 (0.41–0.67)  | 0.95 (0.92–0.96) | 0.59 (0.47–0.70) | 0.94 (0.92–0.95) |
|                                                 | 200                        | 22/373               | 0.43 (0.30–0.56)  | 0.95 (0.92–0.96) | 0.53 (0.40–0.66) | 0.92 (0.91–0.94) |

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

*Polyps were either advanced adenoma or colorectal cancer.

FIGURE 2  Receiver operating characteristic curve to detect colorectal cancer from all adenoma/other bowel conditions/normal with the 95% confidence band. The area under the curve is 0.900 (95% CI 0.844–0.956)

FIGURE 3  Receiver operating characteristic curve to detect advanced neoplasia from nonadvanced adenoma/other bowel conditions/normal with the 95% confidence band. The area under the curve is 0.8251 (95% CI 0.7659–0.8843)
other bowel conditions [normal versus other bowel conditions, 282 (42.28%) vs. 211 (31.83%)]. Hence, the comparison groups in both studies had different characteristics, which could have influenced the outcome. Fourthly, a different FIT kit was used (OC-Sensor versus HM-JACKarc analyser in our study).

The major strengths of this study are its prospective design and direct comparison with endoscopic findings. The comparator groups for CRC, advanced neoplasia and advanced adenoma included participants with a normal colon as well as other pathologies such as diverticular disease and colitis, which reflects the real-life clinical situation.

There are several limitations which could have influenced the outcome of this study. There were a relatively small number of participants in each group. The symptom profiles and comorbidities of the participants were not evaluated. There is contradictory evidence in the published literature suggesting that lower GI symptoms could be associated with false positive FIT results [15,44] and the presence of other medical conditions, such as hypertension, obesity and diabetes, was associated with high false negative rates [27,45]. Notably, a study by Ibanez-Sanz [15] showed that haemorrhoids, anal fissure and upper GI disorders were indeed associated with false positive FIT results. It is also plausible that the chosen cut-off of 90 days for PPI exposure could have altered the outcome. One of the proposed mechanisms by which PPIs affect the FIT is through gut dysbiosis. Studies from the infectious diseases and microbiology literature demonstrated an increased number of recurrent Clostridium difficile infections and bacterial dysbiosis amongst patients who had been on PPIs for 28–90 days. However, there have been no data in the literature so far on the minimum duration of PPI exposure required to alter FIT levels. The duration of PPI exposure prior to FIT testing and the findings on the interaction between the FIT and PPIs, therefore, need to be replicated in a different study population.

In summary, findings from this study show that the FIT can be a good rule-out test at lower thresholds for the detection of both CRC and advanced neoplasia in a population at average risk. Exposure to PPI therapy does not have any effect on the diagnostic yield of FIT. Larger prospectively designed studies in a population-based CRC screening programmes are necessary to determine if the effect of PPI on FIT levels is consistent given the different findings reported within the two populations, namely Spanish and English.
TABLE 3 Estimated coefficient and its standard error by multiple logistic regression in the detection of colorectal cancer and advanced neoplasia from the other conditions

|                                | Estimated coefficient | Standard error | p-value |
|--------------------------------|-----------------------|----------------|---------|
| Colorectal cancer vs. all adenoma/other bowel conditions/normal |                       |                |         |
| Intercept                      | −4.79                 | 1.05           | 0.00    |
| PPI (yes/no)                   | −0.95                 | 0.60           | 0.11    |
| FIT                            | 0.00                  | 0.00           | <0.001  |
| Sex (male/female)              | −0.23                 | 0.39           | 0.55    |
| Age                            | 0.02                  | 0.01           | 0.12    |
| IDA (yes/no)                   | 0.30                  | 0.47           | 0.51    |
| PPI × FIT                      | −0.00                 | 0.00           | 0.98    |
| Advanced neoplasia* vs. nonadvanced adenoma/other bowel conditions/normal |                       |                |         |
| Intercept                      | −3.61                 | 0.78           | 0.00    |
| PPI                            | −0.04                 | 0.31           | 0.88    |
| FIT                            | 0.00                  | 0.00           | <0.001  |
| Sex                            | −0.35                 | 0.27           | 0.19    |
| Age                            | 0.02                  | 0.01           | 0.07    |
| IDA                            | −0.29                 | 0.37           | 0.42    |
| PPI × FIT                      | −0.00                 | 0.00           | 0.43    |

Note: Values for binary variables: Yes =1 and No =0; Male =0 and Female =1.
Abbreviations: FIT, faecal immunochemical test; IDA, iron deficiency anaemia; PPI, proton pump inhibitor exposure.
*Polyps were either advanced adenoma or colorectal cancer.

CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Guarantor of the article: RPA. Specific author contributions: SC, MMW and AF, literature review, patient recruitment, data collection, preparation of manuscript, manuscript editing; SWH and MTA, statistical analysis, manuscript preparation and editing. SS and RPA, design and concept, literature review, critical revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

DECLARATION OF PERSONAL INTERESTS
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ETHICAL APPROVAL
Ethical approval for this study was granted by the Coventry and Warwickshire Research Ethics Committee, UK, as part of the FAMISHED (Food and Fermentation using Metagenomics in Health and Disease) multicentre study (09/H1211/38) and by the London-Bromley Research Ethics Committee, UK, as part of the FAST (FIT in Adenoma Surveillance study) multicentre study (19/LO/1614).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Subashini Chandrapalan https://orcid.org/0000-0002-1582-3224
Ramesh P. Arasaradnam https://orcid.org/0000-0002-2231-3062

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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