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Faecal haemoglobin concentration is related to detection of advanced colorectal neoplasia in the next screening round.

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Abstract

Introduction Relationships between faecal haemoglobin concentrations (f-Hb) below the cut-off used in colorectal cancer (CRC) screening and longer-term outcomes are not well established.

Objectives To examine associations between f-Hb reported as negative and outcomes in the next screening round.

Setting Scottish Bowel Screening Programme.

Methods f-Hb and diagnostic outcomes were investigated for participants with a negative result, f-Hb cut-off < 80.0 µg Hb/g faeces, but then positive within the next two years.

Results Of 37,780 with a negative result, at the next screening round 556 (1.5%) had positive and 30,293 (80.2%) negative results. Initial median f-Hb (2.1 µg Hb/g faeces, IQR: 0.0 - 13.2) was higher in those with a subsequently positive result than those who had a negative result at the next round (0.0 µg Hb/g faeces, IQR: 0.0 - 1.4; $p < 0.0001$). Using f-Hb 0.0 - 19.9 µg Hb/g faeces as reference, logistic regression analysis showed high adjusted OR for advanced neoplasia (AN: CRC or higher-risk adenoma) detection at the next round of 14.3 (95% CI: 8.9 - 23.1) in those with initial f-Hb 20.0 - 39.9 µg Hb/g faeces and 38.0 (95% CI: 20.2 – 71.2) with 60.0 - 79.9 µg Hb/g faeces.

Conclusions A higher proportion of participants with f-Hb of ≥20 µg Hb/g faeces had AN detected at the next round, compared to those with lower f-Hb. Although most relevant when using high f-Hb cut-offs, studies of f-Hb and

outcomes over screening rounds may provide strategies to direct available colonoscopy towards those at highest risk.

Introduction

Participants in colorectal cancer (CRC) screening programmes with faecal haemoglobin concentrations (f-Hb) that are below the selected cut-off for positivity and referral for follow-up colonoscopy, as determined by a quantitative faecal immunochemical test (FIT) for haemoglobin (Hb), are more likely to be diagnosed with an interval cancer (IC) than those with undetectable f-Hb.[1] Rarely documented, however, has been the relationship between a detectable f-Hb below the programme selected cut-off and diagnostic outcome in the longer term. Such knowledge could assist in determining the role of f-Hb as a predictor of the future risk of advanced neoplasia (AN), defined as CRC plus higher-risk adenoma (HRA).

Only two relevant studies have been performed previously. Firstly, in a longitudinal follow-up of CRC screening participants in Taiwan,[2] a cohort of 44,324 participants, aged 40 - 69 years, with f-Hb below the cut-off applied of $\geq$20.0 µg Hb/g faeces were followed for a median of 4.39 years. The incidence of AN rose from 1.75/1000 person-years for those with f-Hb of 0.2 – 3.9 µg Hb/g faeces to 7.08/1000 in those with f-Hb of 16.0 – 19.9 µg Hb/g faeces. Moreover, relative to those with f-Hb of 0.2 – 3.9 µg Hb/g faeces, adjusted hazard ratios (HR) for AN were calculated as 3.41 for those with f-Hb in the category lower than but closest to the cut-off f-Hb used (16.0 – 19.9 µg Hb/g faeces). Secondly, a recent study documents results of regression modelling to further establish the value of f-Hb as a predictor for colorectal neoplasia: [3] 54,921 participants invited between 2001 and 2007 were followed up in the annual FIT-based CRC screening programme in Taiwan to identify

those diagnosed with IC, screen-detected CRC and adenoma. A trend of increasing HR with increasing baseline f-Hb was demonstrated for colorectal neoplasia, including for those with f-Hb above the traditionally used cut-off of ≥ 20 µg Hb/g faeces.

Thus, the available limited evidence indicates that the higher the baseline f-Hb, the greater the likelihood of a future finding of AN. If verified, this could have implications for the design and execution of CRC screening programmes; for example, those with a negative screening test result who are at high risk of having AN by virtue of a detectable f-Hb despite being lower than the cut-off f-Hb applied, could be prioritised for future repeat screening at a shorter interval than the current usual annual or biennial invitation. Conversely, those with undetectable f-Hb, and therefore deemed very unlikely to have a future finding of AN, could perhaps require less frequent invitations to screening. Such a strategy could be an important consideration in countries such as Scotland where, in view of demands on the colonoscopy resource, adoption of a cut-off f-Hb of ≥ 80.0 µg Hb/g faeces (equivalent to ≥ 400 ng Hb/ml buffer) for the planned FIT-based programme is likely, given that this was used in the pilot evaluation required to inform future adoption of FIT as a first-line test.[4] This f-Hb cut-off was selected in order to achieve approximately 2% positivity, to mimic the current screening algorithm based on a two-tier reflex guaiac faecal occult blood test (gFOBT)/qualitative FIT strategy.[4] Since it is known that IC are common at this f-Hb cut-off,[1] it is reasonable to postulate is that a proportion of participants with f-Hb < 80.0 µg Hb/g faeces will have AN detected at the next screening round. Our aim therefore, was to investigate the relationship between f-Hb reported as a negative screening

test result in our FIT evaluation and diagnostic outcomes identified over the two year period of the next screening round to test the hypothesis that those with f-Hb lower than but closer to the cut-off applied are more likely to be subsequently diagnosed with AN.

Materials and Methods

Outside the setting of the FIT evaluation, the Scottish Bowel Screening Programme (SBoSP) uses a two-tier reflex gFOBT/FIT screening algorithm, which has been described in detail previously.[4] The pilot evaluation of using FIT as a first-line screening test in Scotland has also been described in detail previously:[5] all participants with f-Hb ≥ 80.0 µg Hb/g faeces were reported as positive and offered colonoscopy.

Following completion of the FIT evaluation, the SBoSP returned the two NHS Boards to the two-tier reflex gFOBT/FIT screening algorithm. The screening test results for all those eligible to take part in the two years of the next screening round after the FIT evaluation (13 January 2011 to 12 January 2013) and resident in either NHS Tayside or NHS Ayrshire & Arran were examined. The f-Hb from the previous FIT-based pilot evaluation round for those with a positive gFOBT/FIT screening test result was retrieved from the Scottish Bowel Screening IT System (BoSS). Data for colonoscopy outcomes and any subsequent pathology for those with a positive test result were downloaded from the appropriate clinical IT systems in NHS Tayside and NHS Ayrshire & Arran. Data on colonoscopy findings, including number, size,

Dukes' stage, and localisation of CRC and adenomas were collected. As in the SBoSP, HRA were defined as those greater than 10 mm in diameter or when there were three or more adenoma present:[6] AN was defined as CRC and HRA.

MedCalc (MedCalc Software, Mariakerke, Belgium) statistical software was used for all calculations. The Mann-Whitney U test was used for comparison of median f-Hb between classes. Probability of $p < 0.05$ was considered significant. Logistic regression analysis was performed to calculate odds ratios (OR) for diagnosis of AN at the next screening round amongst those in different f-Hb classes and different demographic groups, both adjusted and unadjusted for age and gender as known confounding variables.

Results

The majority of participants (37,780) in the FIT pilot evaluation had an initial negative test result.[5] Of those, 92.7% were eligible for an invitation to further screening with the gFOBT/FIT algorithm: the majority of those not invited were above the age limit applied in the SBoSP (75 years), with others having died or being no longer resident in Scotland. In total, 30,849 participants participated in the FIT evaluation and the subsequent screening round with gFOBT/FIT. Table 1 details the outcomes of all participants who had f-Hb < 80 µg Hb/g faeces, the cut-off used in the FIT evaluation, by age and gender.

Table 1. Number of participants with a negative FIT screening test result and their screening test results in two years in the next gFOBT/FIT screening round.

	All		Men		Women	
	n	%	n	%	n	%
Total with negative FIT screening test result < 80.0 µg Hb/g faeces	37,780		17,525		20,255	
Test result in next gFOBT/FIT round:						
Positive	556	1.5	339	1.9	217	1.1
Negative	30,293	80.2	13,910	79.4	16,383	80.9
Non-responder	4,165	11.0	1,976	11.3	2,189	10.8
Excluded	2,766	7.3	1,300	7.4	1,466	7.2

556 (1.5%) participants had a positive test result in the subsequent screening round and 30,293 (80.2%) had a negative test result. The initial median f-Hb was statistically significantly higher in those who then had a positive test result in the next round than those who remained negative (2.1 µg Hb/g faeces, IQR 0.0 - 13.2 v 0.0 µg Hb/g faeces, IQR 0.0 - 1.4; $p < 0.0001$).

Table 2 shows the diagnostic outcomes, with median f-Hb, of participants who had a positive test result in the next screening round. The differences in median f-Hb between men and women were only statistically significant in those diagnosed at colonoscopy with either non-neoplastic pathology or normal findings (both $p < 0.05$).

Table 2. Diagnostic outcomes and median faecal haemoglobin concentrations (f-Hb) at the initial FIT screening round in participants then having a positive screening test result at the next gFOBT/FIT screening round.

	All				**Men**				**Women**			
	n	%	initial median f-Hb (µg Hb/g faeces)	IQR	n	%	initial median f-Hb (µg Hb/g faeces)	IQR	n	%	initial median f-Hb (µg Hb/g faeces)	IQR
Total positive	556		2.1	0.0 - 13.0	339		1.6	1.2 - 3.0	217		2.4	0 - 12.9
Colorectal cancer (CRC)	26	4.7	16.7	1.2 - 31.6	19	5.6	21.0	0.5 - 36.3	7	3.2	10.2	2.5 - 24.0
Higher risk adenoma (HRA)	85	15.3	13.6	1.2 - 38.5	63	18.6	9.6	0.9 - 38.8	22	10.1	16.6	1.8 - 35.2
Advanced neoplasia (AN: CRC and HRA)	111	20.0	13.6	1.2 - 37.6	82	24.2	14.7	0.8 - 38.8	29	13.4	13.6	1.8 - 35.2
Low risk adenoma	65	11.7	1.7	0.0 - 8.5	42	12.4	1.6	0.0 - 10.9	23	10.6	1.8	0.0 - 7.0
Non-neoplastic pathology	131	23.6	1.6	0.0 - 7.4	72	21.2	0.7	0.0 - 5.8	59	27.2	3.4	0.1 -15.1
Normal findings	169	30.4	1.4	0.0 - 6.2	93	27.4	0.3	0.0 - 5.6	76	35.0	2.0	0.0 - 7.3

Footnote: IQR is the interquartile range (difference between the upper quartile and the lower quartile); non-neoplastic pathology comprises conditions including diverticular disease, haemorrhoids and inflammatory bowel disease and haemorrhoids.

A numerical f-Hb result was available for 30,823 of the 30,849 participants in both screening rounds. The majority of these (96.6%) had f-Hb in the FIT round that was in the lowest class of 0.0 - 19.9 µg Hb/g faeces. 87.4% of participants with a positive gFOBT/FIT result who did not have AN detected were in this low f-Hb class, compared to only 56.8% of those with AN. The proportions of participants with different diagnostic outcomes according to which class of f-Hb they fell into at the initial screening round with FIT are shown in Table 3**.** A lower proportion of participants with previously low f-Hb had AN detected than less severe outcomes, but this trend reversed with rising f-Hb: this is demonstrated in Figure 1. Since a commonly used f-Hb cut-off for screening programmes outside Scotland is $\geq$ 20 µg Hb/g faeces, Table 4 shows further analysis of the class with a f-Hb below this concentration, dissected into two f-Hb classes; those with undetectable f-Hb at the initial FIT screening round and those with f-Hb 1.0 - 19.9 µg Hb/g faeces.

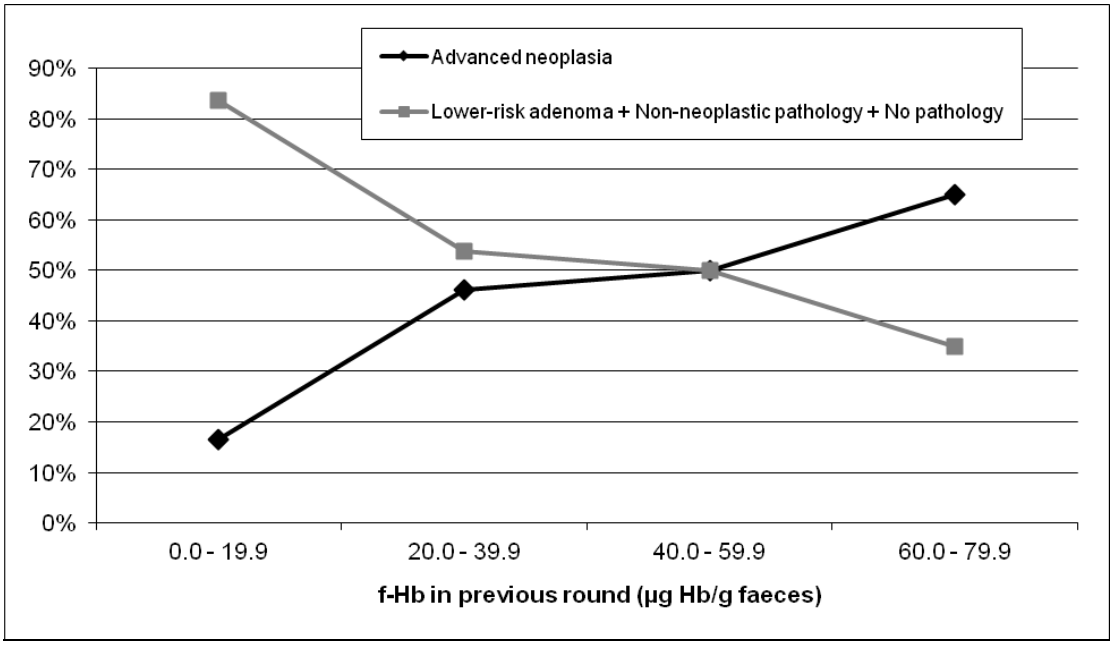
Table 3. Outcomes of participants in both screening rounds according to faecal haemoglobin concentration class at the initial FIT screening round.

	Faecal haemoglobin concentration class in the initial FIT screening round (µg Hb/g faeces)							
	0.0 - 19.9		**20.0 - 39.9**		**40.0 - 59.9**		**60.0 - 79.9**	
Outcome in next FOBT/FIT screening round	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Negative screening test result	29,049	96.6%	661	2.2%	227	0.8%	125	0.4%
Positive screening test result	449	80.8%	59	10.6%	26	4.7%	22	4.0%
Follow-up complete	**383**		**52**		**22**		**20**	

Colorectal cancer (CRC)	14	3.7%	7	13.5%	1	4.5%	4	20.0%
Higher-risk adenoma (HRA)	49	12.8%	17	32.7%	10	45.5%	9	45.0%
Advanced neoplasia (AN: CRC and HRA)	63	16.4%	24	46.2%	11	50.0%	13	65.0%
Low-risk adenoma	58	15.1%	8	15.4%	2	9.1%	0	0.0%
Non-neoplastic pathology	115	30.0%	6	11.5%	7	31.8%	3	15.0%
No pathology detected	147	38.4%	14	26.9%	2	9.1%	4	20.0%

Footnote: Non-neoplastic pathology comprises conditions including diverticular disease, haemorrhoids and inflammatory bowel disease and haemorrhoids.

Figure 1. Percentages of FIT positive screening participants completing follow-up who had advanced neoplasia (AN) or less severe outcomes in the next gFOBT/FIT screening round, according to faecal haemoglobin concentration (f-Hb) class.



Footnote: Non-neoplastic pathology comprises conditions including diverticular disease, haemorrhoids and inflammatory bowel disease and haemorrhoids.

Table 4. Outcomes of participants of both screening rounds with faecal haemoglobin concentration < 20 µg Hb/g faeces at the initial FIT screening round, dissected into two classes.

	Faecal haemoglobin concentration class in the initial FIT screening round (µg Hb/g faeces)			
	Undetectable		1.0 - 19.9	
Outcome in subsequent screening round	n	%	n	%
Negative screening test result	16,621	56.8	12,633	43.2
Positive screening test result	181	40.3	268	59.7
Follow-up complete	**151**		**232**	
Colorectal cancer (CRC)	5	3.3	9	3.8
Higher-risk adenoma (HRA)	14	9.3	35	15.1
Advanced neoplasia (AN: CRC and HRA)	19	12.6	44	19.0
Lower-risk adenoma (LRA)	24	15.9	34	14.7
Non-neoplastic pathology	43	28.5	72	31.0
No pathology detected	65	43.0	82	35.3

Footnote: Non-neoplastic pathology comprises conditions including diverticular disease, haemorrhoids and inflammatory bowel disease and haemorrhoids.

As shown in Table 5, logistic regression analysis showed very high age and gender adjusted OR for AN even in those with f-Hb 20.0 - 39.9 µg Hb/g faeces, using those with f-Hb 0.0 - 19.9 µg Hb/g faeces as the reference group (adjusted OR = 14.3, 95% CI 8.9 - 23.1). Almost one-tenth of all participants who had f-Hb within the highest f-Hb class examined, 60.0 - 79.9 µg Hb/g faeces, and participated in the subsequent round, had AN detected at

the follow-up investigations of a positive test result. AN was over 40-times more prevalent in this class than those with f-Hb previously 0.0 - 19.9 µg/g faeces, of whom 0.21% had AN. The adjusted odds ratio for AN in the highest f-Hb class was calculated to be 38.0 (95% CI 20.2 - 71.2).

Table 5. Odds ratios (both unadjusted and adjusted for age and gender) for advanced neoplasia (AN) found at the next gFOBT/FIT round after a positive screening test result, according to faecal haemoglobin concentration (f-Hb) class in the previous FIT screening round.

f-Hb class (µg Hb/g faeces)	% with AN detected	Odds ratio	
		Unadjusted (95% CI)	Adjusted (95% CI)
0.0 - 19.9	0.2%	1.0	1.0
20.0 - 39.9	3.4%	16.2 (10.1 - 26.2)	14.3 (8.9 - 23.1)
40.0 - 59.9	4.4%	21.5 (11.2 - 41.4)	17.7 (9.2 - 34.2)
60.0 - 79.9	9.0%	45.9 (24.7 - 85.4)	38.0 (20.2 - 71.2)

Footnote: Advanced neoplasia (AN) includes colorectal cancer and higher-risk adenoma.

Discussion

The finding that a higher proportion of participants with a previous f-Hb lower than, but approaching, the cut-off used in our FIT pilot evaluation had AN detected at the next round, compared to those with low f-Hb, provides further evidence that f-Hb is a strong predictor of future risk.

Positivity in those participants who, in the previous round, had f-Hb below the cut-off applied of $\geq$ 80.0 µg Hb/g faeces was 1.5%. This was lower than the overall positivity seen in the FIT pilot evaluation done in Scotland[7] and also with the current gFOBT/FIT algorithm at ca. 2%.[4] This suggests that those who have previously had a negative screening test result, even with a relatively high cut-off f-Hb, are less likely to have a positive test result in the subsequent screening round compared with the overall population invited for screening, which would include first-time participants as well as participants who have previously had a positive test result.

Our findings further support the concept of f-Hb being a valuable predictor of risk of AN since f-Hb was statistically significantly elevated, not only in those who would go on to have a positive test result in the next round compared to those who again had a negative result, but also in those who had AN detected at follow-up investigations compared with those with no pathology (both $p < 0.0001$). Furthermore, one in five participants who had f-Hb in the f-Hb range nearest to the cut-off f-Hb applied and were then positive in the next screening round, were diagnosed with CRC. This compares with one in 27 participants in the lowest f-Hb class examined: thus, those with elevated f-Hb

who go on to have a positive screening test result in the next round are over five times more likely to have CRC detected. When also taking into account detection of HRA, 65% of those participants with a positive screening test result who previously had f-Hb in the highest f-Hb class examined had any AN diagnosed, compared to just 16.4% in the lowest. Moreover, a trend exists of a higher proportion of AN found in participants from each of the four classes of increasing f-Hb. From these data, the odds of having AN detected following a positive screening result are even in those with previous f-Hb between 40.0 and 59.9 μg/g faeces. After this point, it is more likely than not that AN will be present at follow-up investigations in those with a positive screening test result in the next round. Almost one-tenth of all participants with f-Hb approaching the cut-off f-Hb applied went on to have AN detected, representing a 40-fold increase in the risk as compared to those in the lowest f-Hb class. This finding is important when considering f-Hb as a predictor of future risk of AN at the time of a negative screening test result. Not only is strong evidence provided for the value of f-Hb as a risk factor for AN being detected at follow-up investigations of participants going on to have a positive test result, but also for predicting future positivity and the subsequent detection of AN. In addition, since it has been suggested that f-Hb is a predictor, not only of CRC mortality, but also all-cause death,[8] there may be other benefits in the more general application of f-Hb as a predictor of ill health.

If screening programmes collect data such as this, irrespective of the faecal test used, then the effect of cut-off f-Hb on yield of AN can be determined using a graph such as shown in our Figure 1. The f-Hb where the percentage

of participants with positive screening test results completing follow-up who had advanced neoplasia (AN) crosses that of those less severe outcomes can give an indication of the cut-off f-Hb associated with the greatest benefit in terms of yield of advanced neoplasia (AN), although this only includes participants with a positive result at the next screening round and not those who had a negative test result at the subsequent round. CRC screening programmes using FIT have adopted a wide range of f-Hb cut-offs, and the Scottish Bowel Screening Programme FIT evaluation used a much higher f-Hb cut-off than that used in most other countries. Our data allows some comparison of other strategies using lower f-Hb cut-offs. Combining the data presented here with that in our recent publication on IC arising in the cohort participating in the pilot evaluation of screening using FIT,[1] if Scotland used a $\geq$ 60.0 µg Hb/g faeces cut-off rather than the $\geq$ 80.0 µg Hb/g faeces used in the FIT evaluation,[4] then 25.6% additional colonoscopy would yield 20.0% more CRC, or at least possible pre-cursor lesions, presuming these were present at the time of the FIT-based screening. However, in addition to the reduction in the number of false negative screening test results, the number of false positive results will also increase, requiring assessment of the associated harms such as over-diagnosis of lesions that would never have become symptomatic and the risk of complications of colonoscopy.

Further analysis was performed on clinical outcomes at the subsequent screening round of those with an initial f-Hb below the commonly used cut-off f-Hb $\geq$ 20 µg Hb/g faeces. With the prevalence of AN higher in those with f-Hb between 1.0 and 19.9 µg Hb/g faeces than in those with undetectable f-

Hb, evidence is provided that f-Hb is a predictor of future risk of colorectal neoplasia, even at a lower f-Hb cut-off than that used in Scotland.

It is well accepted that men have higher median f-Hb than women.[9,10] Therefore, it is surprising that the median initial f-Hb of participants with a positive screening test result at the next round was higher in women than in men, although this did not reach statistical significance. Significantly higher median initial f-Hb was detected in women compared with men in those with non-neoplastic pathology or normal findings at colonoscopy triggered by a positive screening test result at the next screening round. It appears from this analysis that men who had a false positive screening test result were more likely to have had a low f-Hb in the previous screening round before experiencing short term colonic blood loss to trigger their subsequent positive screening test result. Women, however, may have had longer term colonic bleeding, rising over time. The reasons for this are unclear and may be worthy of further study. Although not statistically significant, median f-Hb of participants with CRC detected at the next screening round was higher in men than in women, but the opposite was apparent for HRA. In fact, previous median f-Hb for women with CRC was very similar to previous median f-Hb of men with HRA. This further demonstrates the variation in f-Hb by gender as documented previously,[9,10] which should be taken into account in setting cut-off f-Hb to be used in any screening programme.

An obvious weakness of this analysis is that different tests were employed in the two rounds screening examined. However, the cut-off employed in the quantitative FIT pilot evaluation was equivalent in terms of positivity to the

current gFOBT/FIT algorithm to which the programme reverted. Of course, it would be of interest to conduct a similar study in which quantitative FIT was used in consecutive screening rounds to allow investigation of the variation in f-Hb over time according to diagnostic outcomes. In addition, the number of CRC cases is low, limiting detailed analysis by sub-groups such as age, gender and lesion site.

Two very recent studies comparing clinical outcomes between two consecutive screening rounds have emerged with very large cohorts allowing sub-analyses by gender and lesion site. Recent work from Spain showed that the second screening round was associated with lower median f-Hb and an increased proportion of proximal CRC.[11] The authors suggested various strategies to improve diagnosis of proximal CRC, such as using a lower cut-off f-Hb at the first compared with the second round. Another study from France has demonstrated that subsequent screening was associated with increased detection of proximal AN, particularly in women, and CRC was more often later stage.[12] Here, it was concluded that, since the late stage CRC were likely to be previously missed lesions, the findings stressed the importance of repeated screening after a previous negative test result. These studies demonstrate the scope that exists for further work into the relationship between f-Hb and outcomes in subsequent screening rounds according to various sub-groups, if working with a large enough sample size.

Our data could impact on CRC screening strategies. Risk scoring models are becoming increasingly developed, with an escalation in published studies in recent years.[13-22] We have confirmed that f-Hb does predict the presence of

colorectal disease through analysis of positivity in the next screening round. In consequence, screening programmes using FIT and looking to apply risk-scoring should certainly incorporate f-Hb into such models, along with age and gender, and perhaps deprivation,[23] to improve their predictive power. The fact that f-Hb is related, not only to colorectal disease severity,[24] but also to future risk, has important implications for FIT-based CRC screening strategies.

Declaration of interests

CGF undertook consultancy with Immunostics Inc., Ocean, NJ, USA, Mode Diagnostics, Glasgow, Scotland, and Kyowa-Medex, Tokyo, Japan. All other authors had no conflicting interests.

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Research Ethics

Ethical approval was not required for this study. It was approved by the Programme Board, Scottish Bowel Screening Programme.

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