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**Review**

**Strategies to minimise the current disadvantages experienced by women in faecal immunochemical test-based colorectal cancer screening**

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## Abstract

Currently, women are disadvantaged compared to men in colorectal cancer (CRC) screening, particularly in programmes that use faecal immunochemical tests for haemoglobin (FIT) followed by colonoscopy. Although there is no single cause for all the known disadvantages, many can be attributed to the ubiquitous finding that women have lower faecal haemoglobin concentrations (f-Hb) than men; there are many plausible reasons for this. Generally, a single f-Hb threshold is used in CRC screening programmes, leading to lower positivity for women than men, which causes poorer outcomes for women, including lower CRC detection rate, higher interval cancer (IC) proportion, and higher CRC mortality. Many of the now widely advocated risk scoring strategies do include factors taking account of sex, but these have not been extensively piloted or introduced. Using different f-Hb thresholds for the sexes seems advantageous, but there are difficulties, including deciding which characteristic should be selected to achieve equivalency, for example, positivity, IC proportions, or specificity. Moreover, additional colonoscopy resources, often constrained, would be required. Governments and their agencies should be encouraged to prioritise the allocation of resources to put simple strategies into practice, such as different f-Hb thresholds to create equal positivity in both sexes.

## Introduction

Colorectal cancer (CRC) remains a significant global health problem as the third most commonly diagnosed and second most common cause of cancer death in the world. [1] Several studies have shown that CRC incidence and mortality have been steadily decreasing for at least two decades in many high-income countries in Northern America, Oceania, and Northern and Western Europe but, in contrast, significant increases have been seen in incidence and mortality rates in less developed countries in Asia, Africa, and Latin America. [2] It may be that, if longevity in high-income countries increases, CRC incidence will also increase in these in the future. [2] The decreases in incidence and mortality in high-income countries are undoubtedly due to advances in endoscopy and in the treatment of detected CRC but also, importantly, to early detection through screening as a result of the removal of adenomatous polyps and identification of early stage disease. [3] A number of strategies can be implemented for both opportunistic and programmatic CRC screening. [4] Faecal immunochemical tests for haemoglobin (FIT) are now the most commonly used initial non-invasive approach [5] and their analytical [6,7] and clinical [8,9] characteristics have been recently reviewed: a positive FIT result, that is a faecal haemoglobin concentration (f-Hb) above the chosen threshold, is followed by colorectal visualisation, conventionally colonoscopy.

It is well documented that there are a number of important sex differences in CRC screening. For example, many publications show that uptake of FIT is higher in women than in men, as demonstrated in Scotland [10] and England. [11] In the UK, fewer women than men develop CRC, with published age-standardised incidence

rates lower in women than in men and CRC mortality rates also lower in women. [12] This review documented that, while there were relatively small differences in routes to diagnosis of CRC to 5-year survival for women and men, the lower CRC death rate in women is primarily due to the lower incidence rate. The lower mortality of CRC in women appeared to be a result of exogenous and/or endogenous factors pre-diagnosis that led to this lower incidence rate. [12] Indeed, globally, there is a trend for women to have both lower CRC incidence and mortality. [13] But, taking all the evidence into account, there is no doubt that women are disadvantaged in CRC screening with FIT when a single faecal f-Hb is applied in a screening programme for all participants and colonoscopy is used for follow-up investigation.

### **Aims, objectives, and methodology**

The aims and objectives of this review are to (a) collate the existing evidence on why women are disadvantaged in conventional two-step CRC screening, that is FIT at a single f-Hb threshold for all participants, followed by bowel visualisation, conventionally colonoscopy, (b) suggest possible reasons for these documented disadvantages, (c) detail the plausible explanations as to why women have lower f-Hb than men, (d) document possible approaches to minimise or eliminate sex inequality, and (e) document simple and realistic strategies for improvement of current practice.

The structure of this work is such that is not a systematic review and meta-analysis performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach, since PRISMA is an evidence-based minimum

set of items for reporting which primarily focuses on the publication of reviews evaluating the effects of interventions. [14]. Our approach is that, mainly using PubMed in an ongoing strategy, we closely follow the publication of relevant materials using “faecal occult”, “faecal immunochemical”, “faecal haemoglobin”, “colorectal cancer screening” and these terms with “sex” and “gender”. In addition, all the citations contained in found relevant publications are then assessed for significance to the topic of this review.

### **Women are disadvantaged in conventional initial FIT CRC screening**

At a single f-Hb threshold followed by colonoscopy, the evidence that women are disadvantaged encompasses many facets of CRC screening. In addition, women are disadvantaged through other mechanisms. A comprehensive list follows and a summary is shown in Table 1.

FIT positivity is lower in women than for men, meaning a smaller percentage of women participants are invited for further investigation. As one example, in a ground-breaking study done in Spain, using a single sample FIT on 444,582 invited average-risk subjects aged 50-69 years, a result was considered positive at  $\geq 20 \mu\text{g Hb/g}$  faeces. Outcome measures were analysed by sex and age for a wide range of f-Hb thresholds. Participants with f-Hb above the threshold (17,387) in the screening programme underwent colonoscopy. Participation rate was 66.5%. Women had a positivity of 4.8% and men 8.3%. [15]

Although the uptake of, and adherence to, screening is consistently higher than that in men, the yield of neoplastic pathology is lower in women as shown in the Spanish study [15] and, in a study in England, also using a f-Hb threshold of  $\geq 20 \mu\text{g Hb/g}$  faeces, the overall CRC detection rate in the English study was 0.27% and the rate for advanced adenoma was 1.73%, but the detection rates of CRC and of advanced adenomas were more than half as low in women as in men. [11]

The interval cancer (IC) proportion, that is CRC that are detected after the finding of a f-Hb below the applied threshold but before the next invitation to screening, is higher in women than in men, particularly when a high f-Hb threshold is used due to constrained colonoscopy capacity. [16] Further, in a recent study, IC occurred more frequently in women aged 70-74 years, and were more often right-sided, advanced stage, and high grade. [17]

An international study confirmed that a notable proportions of patients with CRC are diagnosed through emergency presentations: a higher percentage of colon cancers presenting as an emergency were women (35.0%) as compared to men (33.8%). A difference was also seen in rectal cancer with 15.6% of women as compared to 13.2% of men presenting as an emergency. [18]

The nosological characteristics of FIT have been well documented. In a study in California, at the widely used f-Hb threshold of  $\geq 20 \mu\text{g Hb/g}$  faeces, the screening programme sensitivity was lower in women (70.6%) than men (77.0%). [19] FIT performance in women and men was investigated in a prospective cohort study in The Netherlands, in which a total of 10,008 average-risk subjects (aged 50-74 years)



were invited for first-round CRC screening and 8316 average-risk subjects (aged 51-74 years) were invited for second-round screening using a f-Hb threshold of  $\geq 10 \mu\text{g}$  Hb/g faeces. The detection rate of advanced neoplasia was 2.2% for women and 4.4% for men in the first round. The positive predictive value (PPV) for advanced neoplasia in the first round was 37% for women and 42% for men. However, a significantly lower false-positive rate was seen in women (4.1%) than in men (6.3%). Similar differences in these test characteristics were seen in the second round. [20]

In another study from The Netherlands, at a range of f-Hb thresholds, FIT sensitivity for CRC was lower and specificity was higher in women compared to men. At a f-Hb threshold of  $\geq 15 \mu\text{g}$  Hb/g faeces, sensitivity for CRC was 71% in women and 93% in men and specificity was 93% in women as compared to 90% in men. Sensitivity for advanced adenomas was 29% in women compared to 33% in men and specificity was 95% in women as compared to 93% in men. It was concluded that equality of test characteristics could be achieved using different f-Hb thresholds for the sexes. [21]

At the f-Hb threshold recommended by the manufacturer ( $17 \mu\text{g}$  Hb/g faeces), higher negative predictive values (NPV) were observed among women compared with men (94.7% vs 92.5%). Specificity was also higher among women compared with men (94.7% vs 92.3%, while there was only a little variation in sensitivity (40.3% vs 41.8%) according to sex. [22]

FIT performance for detection of advanced colorectal neoplasia by sex was evaluated across nine different FIT brands in a colonoscopy-controlled setting. Sensitivity was consistently lower, and specificity was consistently higher for women as compared to men. It was suggested that comparisons of measures of diagnostic performance among studies with different sex or age distributions should be interpreted with caution. [23]

It has been suggested that fewer false positive FIT results (7.0%) are found in women as compared to men (9.5%), [24] in contrast, a recent systematic review and meta-analysis of studies with 54,499 participants showed that women have a significantly higher risk of false positivity, increasing colonoscopy demand without increasing CRC detection. [25]

The f-Hb in women found to have CRC as a result of FIT screening are lower than in men and this is true stage for stage and site for site within the colorectum. [26]

It is well documented that FIT-based screening programmes are associated with a lower CRC incidence and mortality reduction in women than in men: for example, in the Emilia-Romagna Region there was an incidence reduction of 21% among women and 33% among men, and mortality reduction of 54% and 65%, respectively. [27]

CRC location is different between women and men, with women showing more adenomas located in the proximal colon. [28] Moreover, a larger proportion of women develop flat and depressed type colorectal neoplasia, which can remain undetected and lead to late diagnosis, in contrast to men, who more commonly develop polypoid type of neoplasia that is more easily detected and resected. [29] Although, the significance of sessile serrated lesions (SSL) on the burden of CRC is less well documented than other neoplastic lesions, it has been shown that SSL detection was significantly higher in women compared with men (16.2% v 11.7%, particularly in those aged <50 years (16.8% v 8.6%); [30] since the sensitivity for SSL using FIT is low [31], women are again likely to be disadvantaged. A review has

documented that patients with right-sided CRC were more often women as well as older, possibly with more co-morbidities, more advanced tumour stages, increased tumour sizes, more poorly differentiated tumours, different molecular biological tumour patterns, and a poorer prognosis than those with left-sided CRC. [32]

Post colonoscopy CRC (PCCRC) rates are higher in women than in men. In a study in England, the unadjusted PCCRC three year rate was 7.4% (9317/126152), and rates were higher not only in women, but also in older age groups, and in people with inflammatory bowel disease or diverticular disease, in those with higher comorbidity scores, and in people with previous cancers. [33]

Colonoscopy is more difficult in women and, in consequence, there are more incomplete colonoscopies after a positive FIT result in women, leading to less advantageous outcomes than in men. [34]

As described in a recent review, a number of other factors may inhibit women from attending for colonoscopy, leading to poorer outcomes, including that women might be more embarrassed to undergo colonoscopy, especially when the procedure is performed by a male endoscopist and, in some countries, there are more male than female endoscopists. [35]

**Why are women disadvantaged?**

Although it is considered that there is no unifying single hypothesis, plausible reasons for this wide spectrum of findings which provides considerable evidence that women are disadvantaged in FIT-based screening include the following.

Women have lower CRC incidence than men and therefore CRC and adenoma rates in screening are likely to be lower, as has been found in practice. [36]

As discussed above, women have a higher proportion of right-sided CRC than men and the consequences of this may be degradation of any faecal haemoglobin present in the lumen as the faeces forms when passing through the colorectum: this is further discussed in detail below. Moreover, right sided CRC may bleed less because they are more likely to be sessile than polypoid. [37]

Although there is much debate about lowering the age at which CRC screening should commence in view of the rising incidence in younger individuals, [38] the age range for first invitation for women is generally the same as for men. There are a number of studies which postulate that CRC screening should start at a higher age in women than in men. A detailed exploration of cumulative 10-year incidence and mortality of CRC reached among women at ages 50, 55, and 60 years found that men mainly reached equivalent levels when 4 to 8 years younger: the sex differences seen were remarkably constant across populations and over time. [39] More recently, it has been suggested that, where resources are constrained and it is not feasible to screen everyone from the currently usual recommended age of 50 years, starting screening later in women than in men was likely to be more cost-

effective and gain more health benefits overall than strategies where women and men start screening at the same age. [40]

Most importantly, the f-Hb is lower in women than in men in all countries studied [41-44] and in different regions of a single country and also using different FIT analytical systems, [45] and also in women and men found to have CRC. [26] meaning as stated above, that positivity will be lower in women than in men and that a single f-Hb threshold will dissect out fewer women than men for further investigation.

### **Why do women have lower faecal haemoglobin concentrations than men?**

The lower f-Hb in women than in men provides a good explanation as to why the positivity in FIT-based screening is lower in women than in men and this clearly has ramifications on many of the other characteristics and outcomes documented above that influence outcomes in women and men. The reasons for the lower f-Hb in women could include the following.

Blood haemoglobin concentrations are lower in women than in men, but these differences do disappear after the menopause, when screening usually commences. [46]

Women and men have different CRC incidence age profiles: f-Hb is dependent on age, the higher the age, the higher the f-Hb. [47]

Women have a longer gut transit time than men, [48] and slower gut emptying, leading to higher levels of degradation of any haemoglobin which is released into the colon, and lower detection of right-sided neoplastic lesions, since faecal haemoglobin degrades *in vivo*. [7] In addition, women have more constipation than men, again leading to higher levels of degradation of any haemoglobin present in the colon. [49]

Women have longer colon lengths than men again possibly causing more degradation of any haemoglobin in the colon in women as compared to men. [50]

Generally, women have healthier lifestyles than men and, in consequence, they have less chronic disease which has been shown to be associated with higher f-Hb without findings of rectal bleeding on colonoscopy. [51] However, if women are simply healthier overall, the lower f-Hb due to the absence of the systemic inflammation of chronic disease would not disadvantage them in CRC screening.

### **How can sex inequality be minimised or eliminated?**

Recently, it has become more widely appreciated that women are disadvantaged in CRC screening programmes using FIT at a single f-Hb threshold for all participants. and several rather different strategies seem possible to enhance equality.

### ***Risk-scoring***

There are many suggestions that risk scoring approaches could be advantageous. These have been addressed in a superb comprehensive recent review in which 102 unique studies were examined. Overall, the results showed that risk-stratified CRC screening programmes could potentially improve diagnostic performance, but there was a paucity of information on longer-term outcomes. Moreover, it was stated that, despite over 20 years of studies and growing calls for the routine introduction of risk stratification strategies, only a limited number of studies have actually piloted such approaches. A number of studies have involved examination of the efficacy of the risk-based screening approaches in comparison, and/or combination, with FIT but the review concluded that it is difficult to draw definitive conclusions about these particular approaches since the results were mixed. [52] A recent research topic of much interest and relevance is that polygenic risk scores (PRS) are increasingly suggested of being of value for risk stratification in CRC screening; however, as found in a recent study, even in combination with FIT, using with PRS did not improve diagnostic accuracy of FIT-based screening in a large asymptomatic CRC screening population. [53]

### ***Internet risk calculators***

There are a number of simple calculators available on the Internet. These can be accessed by the public. Examples include Colorectal Cancer Risk Assessment from the University of Rochester Medical School, [54] the Colorectal Cancer Risk Assessment Tool from the National Cancer Institute (USA), [55] What's my risk? Colorectal Cancer from Cancer Care Ontario, [56] and the QCancer 15 year risk calculator, [57] and there are many more. A range of variables is included in these

including sex to cater for the known differences between women and men, age, weight, height, activity, dietary habits, smoking habits, alcohol intake, and personal and family medical history. Interestingly, identical data entered into these and other calculators do not give the same scores. Some include questions on whether a gFOBT or FIT has been done but, to our knowledge, a quantitative f-Hb result has never been included in such calculators, although it has been very well documented that f-Hb is directly related to colorectal disease severity. [58] An interesting question is whether participants in screening (and patients presenting with lower bowel symptoms) should be given the numerical f-Hb found; after all, individuals currently monitor their own weight, blood pressure, blood glucose, and even faecal calprotectin, an index of bowel inflammation. [59]

### ***Evidence to support the use of stratified f-Hb thresholds for women and men***

Although the use of different f-Hb thresholds for women and men have been suggested for many years, it is only recently that experiences have informed on the value of this. Research evidence of value include a number of studies.

Data from a study of 1,112 asymptomatic average-risk screening participants undergoing colonoscopy without preselection were used to build a logistic regression model to calculate the risk of having advanced neoplasia at colonoscopy using age, sex, and f-Hb as variables. A risk threshold that would produce a specificity of 96.9% in the study group was set, matching the specificity of FIT at a cut-off of  $\geq 20$   $\mu\text{g}$  Hb/g faeces. At this threshold, age- and sex-adjusted FIT cut-off concentrations ranged from 36.9  $\mu\text{g}$  Hb/g faeces for 50-year-old women to 9.5  $\mu\text{g}$  Hb/g faeces for 75-year



old men. Using a risk threshold instead of a uniform f-Hb threshold for inviting screening participants to follow-up colonoscopy ensured that all participants had a comparable risk prior to colonoscopy. [60]

In a multicentric retrospective cohort study of participants in CRC screening programmes, receiver operator characteristic (ROC) curves were used to identify the optimal f-Hb threshold for each age and sex group. *Inter alia*, the optimal f-Hb thresholds for women were 18.3 µg Hb/g faeces (for 50-59 years) and 14.6 µg Hb/g faeces (for 60-69 years), and 16.8 µg Hb/g faeces (for 50-59 years) and 19.9 µg Hb/g faeces (for 60-69 years) for men. It was concluded that the optimal f-Hb threshold varies for different sex and age groups and the use of these for each of the four groups improves sensitivity and leads to a small decrease in interval cancers, but also to an increase in false positive results. [61]

A Danish study was aimed at assessing the relative effectiveness in removal of adenomas and detection of cancer of implementing CRC screening in different demographic and socioeconomic groups. As expected, the relative risk of having adenomas removed was lower among women compared to men and detection of CRC was lower among women compared with men. [62] A further study from Denmark concluded that it is possible to decrease the number of needed colonoscopies while at the same time increase the overall sensitivity and specificity by using different f-Hb thresholds for men and women and for different age groups. This would, however, increase the inequality in sensitivity and specificity, and, due to this, other strategies such as ensuring equal sensitivity could be considered. [63]

### ***Stratified f-Hb thresholds for women and men in practice***

Recently, the results of the application of f-Hb stratified by sex in routine practice have appeared. A report from Finland showed that, using f-Hb thresholds of  $\geq 25$   $\mu\text{g}$  Hb/g faeces for women and  $\geq 70$   $\mu\text{g}$  Hb/g faeces for men gave similar CRC detection rates in both sexes (0.16% for women and 0.18% for men) and similar PPV for CRC (6.4% for women and 6.6% for men). [64] However, in this study, the positivities in women and men using these f-Hb thresholds were 2.6% and 2.4%, respectively, considerably lower than those currently reported in many countries at similar f-Hb thresholds, perhaps due to demographic factors such as the age range of participants and lifestyle, and also perhaps because f-Hb found are highly dependent on the FIT system employed, [65,66] so the results from Finland may not necessarily be transferable over geography.

A study done in Sweden investigated participants in CRC screening using f-Hb concentration thresholds of  $\geq 40$   $\mu\text{g}$  Hb/g faeces in women and  $\geq 80$   $\mu\text{g}$  Hb/g faeces in men. The yield of CRC was assessed and compared to a threshold of  $\geq 80$   $\mu\text{g}$  Hb/g faeces (as used in Scotland at the present time) in both sexes. Positivity in this Swedish study was 2.7% in both sexes but, in this case, the PPV for CRC was significantly lower in women (5.8%) than men (8.3%). "Negative" colonoscopies were, therefore, more common in women (24%) than in men (17%) but, in 120 women with CRC, 23.3% had f-Hb  $\leq 80$   $\mu\text{g}$  Hb/g faeces. In consequence, it was concluded that the high rate of CRC detected in women using the lower f-Hb threshold outweighed the minor increase in screening costs incurred by using sex

stratified f-Hb thresholds. [67] In a further report on the population-based screening programme in Stockholm-Gotland with f-Hb thresholds of  $\geq 40$   $\mu\text{g}$  Hb/g faeces in women and  $\geq 80$   $\mu\text{g}$  Hb/g faeces in men, the FIT sensitivity was higher and the IC rate was lower in women. [68] This might imply that raising the f-Hb threshold in men, while perhaps advantaging women by freeing up colonoscopy resource and facilitating a lower threshold, would, in our opinion, certainly disadvantage men.

### **Strategies for improvement**

It is clear that women are disadvantaged as compared to men in many aspects of CRC screening, especially in those programmes that use FIT as a first-line test with a single f-Hb threshold for all participants and then follow up positive test results with colorectal visualisation, usually colonoscopy. There is now evolving evidence from both research and routine practice that sex stratified f-Hb thresholds for women and men could minimise current sex differences and it seems now widely advocated that this would be an easy strategy to introduce or, perhaps better, pilot, although it should be recognised that pilots may confound as well as inform. [69] However, there are difficulties.

Firstly, it would be difficult to decide which performance characteristic is most desirable to have sex equality, for example, sensitivity, specificity, positivity, PPV, NPV, IC proportion, CRC detection rate, adenoma detection rate, or other? This is important because the f-Hb thresholds for women and men selected will differ depending on the characteristic chosen for sex equalisation. For, example, in Scotland, the f-Hb threshold currently used for all participants is  $\geq 80$   $\mu\text{g}$  Hb/g faeces

and, to have equal positivity, the f-Hb threshold for women would have to be  $\geq 50 \mu\text{g}$  Hb/g faeces if, an important consideration, men were not to be disadvantaged as compared to the current Scottish Bowel Screening Programme. [45] In contrast, should it be considered that IC proportions should be equal in women and men, then the f-Hb threshold for women would have to be  $\geq 40 \mu\text{g}$  Hb/g faeces. [70] However, it would be difficult to rapidly assess the effect of introducing sex related f-Hb thresholds except for positivity; this is our favoured strategy at this time.

Secondly, if the f-Hb threshold for women was lowered, the colonoscopy requirement would be increased, a real problem for colonoscopy constrained countries. An alternative, in order to keep colonoscopy requirements constant, the f-Hb threshold used for men could be increased, but this would lower the positivity for men and would consequently disadvantage them as compared to current approaches. Interestingly, governments and their departments and agencies, and charities, do not seem to have recognised that there is a problem of sex inequality in current CRC screening programmes. For example, in Scotland, on 20 August 2021, the Scottish Government published the Women's Health Plan: Tackling inequalities and improving health. [71] The document states: cancer screening remains a priority and we will continue to deliver our Screening Inequalities Fund to tackle inequalities in the national population screening programmes, setting aside £2 million over the next two years. The three areas on which activity will be focussed are: self-sampling in the cervical screening programme, the breast screening programme review, and ongoing work to address inequalities, mainly those due to socio-economic factors. However, the current sex inequalities in the Scottish Bowel Screening Programme were not addressed. Perhaps this is because, in this very successful screening

programme, women do have higher participation than men, above the target of 60%. In addition, it may be that Scottish Government was unaware of the issues. However, perhaps some of the allocated funding and increased effort earmarked for cancer and women's health could be directed to this very simple strategy to enhance women's health throughout Scotland. And perhaps this simple strategy for reducing existing sex inequality should be a priority for some of the considerable additional resources earmarked for endoscopy in the recent Scottish NHS Recovery Plan. [72] Moreover, the cancer charities and the media must be made more aware of the current situation and put pressure on the organisers and funders of programmatic CRC screening efforts to reduce current sex inequalities.

Finally, countries that use FIT in the assessment of patients who present in primary or secondary care with lower abdominal symptoms may be enhancing sex inequality by adopting different f-Hb thresholds for referral for bowel visualisation in symptomatic patients and in screening programmes. FIT are very different in these two clinical settings, [73] and, for example, in Scotland  $\geq 10 \mu\text{g Hb/g}$  faeces is used in assessment of patients with symptoms [74] as recommended in the National Institute for Health and Clinical excellence guideline DG30 on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care, [75] but currently  $\geq 80 \mu\text{g Hb/g}$  faeces is used as the threshold in the Screening Programme, a f-Hb threshold higher than in most countries using FIT-based approaches for screening. Higher f-Hb thresholds are used in the screening programmes of the other three UK nations. Interestingly, in the assessment of symptomatic patients, sex differences may exist, although probably not as telling as those found in screening. For example, in one study, there did not seem to be a significant sex difference for

missed CRC at the very low threshold of 2  $\mu\text{g}$  Hb/g faeces, but there might be a difference at 10  $\mu\text{g}$  Hb/g faeces. [76] Thus, and this is admittedly conjecture, if a woman has participated in a screening programme and has a “negative” FIT result which was recorded on her electronic medical record as such, will health care professionals consider, if a consultation is made for lower abdominal symptoms, that CRC is unlikely because of this result, not undertake a new “symptomatic” FIT with the far lower f-Hb threshold, and go down other clinical pathways to investigate other very common problems of women during reproductive and post-menopausal stages of life that present with abdominal symptoms? Perhaps studies of this speculative concept, and/or further education of health care professionals on the merits and demerits of FIT, especially in women, are warranted. Use of f-Hb data have come of age, but further maturation seems desirable. [77] In the multi-disciplinary teams that are essential for the organisation and delivery of CRC screening programmes, professionals in laboratory medicine should play important roles in facilitating these exciting possibilities. [78]

## **Conclusions**

Women are undoubtedly disadvantaged compared to men in CRC screening, particularly in programmes that use FIT followed by colonoscopy, as summarised in Table 1. There is no single plausible cause for all the known disadvantages, but many can be attributed to women having lower f-Hb than men. A single f-Hb threshold is generally used in CRC screening programmes, giving lower positivity for women than men, which leads to a range of poorer outcomes for women. Risk scoring strategies, an approach now widely advocated, often include sex-related

factors, but these have not been extensively piloted or introduced. Using different f-Hb thresholds for the sexes seems advantageous, but there are difficulties, including deciding which characteristic or outcome to choose to achieve equivalency.

Moreover, additional colonoscopy resources, often constrained, would be required.

The allocation of resources to put simple strategies into practice, such as different f-Hb thresholds to create equal positivity in both sexes, should be encouraged.

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### **Author contributions:**

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RJCS is Clinical Director of the Scottish Bowel Screening Programme since its inception in 2000 and provided significant input into the sections on screening and colonoscopy. CGF organized and supervised the screening laboratory from 2000-

2010 and wrote the first draft of this manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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**Table 1.** Summary of the disadvantages experienced by women as compared to men in faecal immunochemical test (FIT), followed by colonoscopy, colorectal cancer screening programmes.

FIT positivity is lower in women than for men: thus, a smaller percentage of women participants are invited for further investigation.
Although the uptake of, and adherence to, FIT screening is consistently higher than that in men, the yield of neoplastic pathology is lower in women.
The interval cancer proportion, CRC that are detected after the finding of a FIT result below the threshold but before the next screening invitation, is higher in women.
A higher percentage of colon cancers presenting as an emergency are women as compared to men; a similar difference is also seen in rectal cancer.
FIT clinical sensitivity is consistently lower, and clinical specificity is consistently higher, for women as compared to men.
Women have a significantly higher risk of false positive FIT results leading to unnecessary colonoscopy.
The FIT results in women found to have CRC as a result of FIT screening are lower than in men.
FIT-based screening programmes are associated with a lower CRC incidence and mortality reduction in women than in men.
CRC location is different between women and men, with women showing more adenomas located in the proximal colon.
Sessile serrated lesion detection is significantly higher in women compared with men; such lesions are not well detected by FIT.
Post colonoscopy CRC (PCCRC) rates are higher in women than in men.
Colonoscopy is more difficult in women and, in consequence, there are more incomplete colonoscopies after a positive FIT result in women.
A number of other factors may inhibit women from attending for colonoscopy, leading to poorer outcomes.