Editorial



# Faecal haemoglobin concentration and personalised assessment of the risk of colorectal neoplasia

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## Introduction: colorectal cancer (CRC) screening

Since it is the third most common cancer developed and the fourth cause of cancer related death worldwide, CRC still presents a major health problem (1). However, if colorectal neoplasia is detected at an early stage, outcomes for individuals are much improved (2). Asymptomatic population-based screening programmes for colorectal neoplasia have been widely introduced since the criteria for successful screening are more than met. Early CRC is detected and removal of adenomas, which are sometimes precursors of CRC, is expedited. In addition to the wide beneficial modification to lifestyles that has ensued over recent years, screening is considered to be a major cause why both the incidence and mortality of CRC is now decreasing, at least in well developed countries (3). There are many possible approaches to CRC screening (2), but faecal immunochemical tests (FITs) for haemoglobin are currently considered the non-invasive investigation of choice and are recommended in guidelines promulgated in very many countries (4).

## FITs for haemoglobin

FITs are available in two formats, qualitative, generally based on immunochromatographic test strips or cassettes, and quantitative, generally based on immunoturbidimetry, often performed on small benchtop closed systems, although one manufacturer supplies reagents and calibrators that can be used on a range of open clinical chemistry analytical systems (5). Qualitative FITs are often used when individual opportunistic screening opportunities arise, whereas quantitative FITs are widely used in programmatic population-based screening. Quantitative FITs have many advantages, a major benefit being that examinations on faecal samples allow generation of estimates of the faecal haemoglobin (f-Hb) concentration (6). The f-Hb cut-off to be applied in CRC screening programmes can then be selected on, for example, consideration of the available colonoscopy resource. Research has explored many basic aspects concerning f-Hb and it has been shown that f-Hb rises with age and is higher in men than in women (7,8), and higher in the more socioeconomically deprived (8,9). It has been well documented that higher f-Hb is associated with a higher incidence of CRC and advanced adenoma, that is, advanced neoplasia (AN), because f-Hb is directly related to the severity of colorectal disease (10). Thus, it is hardly surprising that, if FITs are used as a simple qualitative dichotomous investigation with a single cut-off f-Hb applied to all participants, as is done in almost all current CRC screening programmes, as the f-Hb cut-off applied is increased, positivity rate, AN detection rate and sensitivity decrease, while specificity, positive predictive value and interval cancer proportion increase.

## f-Hb concentration and risk

Some time ago now, it was shown by Chen *et al.* that f-Hb at first screening predicts subsequent risk of incident colorectal neoplasia and it was suggested that, during follow-up, risk stratification based on f-Hb could help clinicians,

with particular attention being paid to those with higher initial f-Hb, especially those just under the f-Hb cut-off applied (11). This work has been subsequently extended and f-Hb has been demonstrated to be an independent predictor of the risk of colorectal neoplasia (12). In Scotland, it has been documented that f-Hb is related to detection of AN in the next screening round and it was clearly stated that studies of f-Hb and outcomes over screening rounds might provide strategies to direct available colonoscopy towards those at highest risk (13). Indeed, over recent time, there has been much interest in improved use of the numerical data on f-Hb that can be generated from quantitative FITs, particularly in personalised risk assessment. It has been suggested that a personalised approach to screening could enable those at greatest risk to be referred for colonoscopy, optimising resource use and ultimately individual outcomes: this recent opinion piece detailed some interesting concepts and the work supporting this potentially useful risk-scoring approach to CRC screening (14). In addition, a comprehensive systematic review of risk prediction models that could be used for personalisation of screening strategies has been recently published, although few to date actually incorporate f-Hb, probably the most relevant variable in assessment of risk (15).

## f-Hb concentrations below the programme applied cut-off

These concepts have been considerably supported through the recent study of Grobbee *et al.* (16), which investigated the association between f-Hb below the cut-off used in the screening studies from The Netherlands, namely 10 µg Hb/g faeces, and later development of AN. The study investigated 9561 average-risk subjects (aged 50–74 years) who were offered four rounds of FIT-based screening from November 2006 through December 2014. Data from 7,663 participants screened at least once and found to have a result below the f-Hb cut-off were followed for a median of 4.7 years. After eight years of follow up, participants with baseline concentrations of 8–10 µg Hb/g faeces had a more than six-fold higher cumulative incidence of AN than participants with 0 µg Hb/g faeces Multi-variate hazard ratios increased from 1.2 for subjects with f-Hb of 0–2 µg Hb/g faeces to 8.2 for subjects with concentrations of 8–10 µg Hb/g faeces and participants with two consecutive f-Hb of 8 µg Hb/g faeces had a 14-fold increase in risk of AN compared to participants with two consecutive f-Hb of 0 µg Hb/g faeces.

This very impressive work led to the suggestion that that application of these findings might be used in designing personalised strategies for population-based CRC screening and reduce unnecessary repeat tests. The results unequivocally support the concept that an individual f-Hb below the programme applied cut-off in a first round of screening is an independent predictor for the risk of incident AN. Furthermore, it was proposed that consecutive low f-Hb could be used in determining personalised screening strategies. It would be difficult to disagree that these findings point to much better ways to use f-Hb than the current single f-Hb cut-off applied to all approach.

It was also stated that the results could aid in informing patients about the risk of AN after multiple f-Hb below the applied cut-off (traditionally reported as negative, normal or low-risk), and to alter screening intervals accordingly. This opens up some interesting potential approaches for the future, but also poses some dilemmas.

Would readily available data such as age and sex, which have been shown to affect f-Hb (7,8) be usefully incorporated in a risk-based screening algorithm as suggested a number of times (14,17) and already shown to be potentially useful in use of f-Hb in the assessment of patients presenting with symptoms of CRC (18). This would be both simple and inexpensive but, as suggested, further research is necessary to determine the benefits of more complex algorithms incorporating variables other than f-Hb (14).

How should the results for individuals be reported? Currently, those with f-Hb higher than the applied programme cut-off are offered further investigations, usually colonoscopy, and those with f-Hb below the cut-off are reassured, given health and lifestyle advice, and re-invited at the screening interval adopted by the programme. Should individual f-Hb be reported to screening programme participants? This would certainly involve significant improvement to current communication strategies, particularly since the concept of risk seems poorly understood. Should participants "know their number" and decide on further investigation themselves as an informed choice?

If an individual had a f-Hb that is considered to be of some risk, but does not wish to undergo further invasive, unpleasant and potentially harmful further investigation, would modification of lifestyle factors known to affect CRC, such as intake of meat, alcohol consumption, exercise taken, smoking habits and body mass index, result in reduction of f-Hb and, in consequence, risk of future AN?

It was suggested by Grobbee *et al.* (16) that, over the course of multiple screening rounds, serial f-Hb could then

 

be of guidance in identifying those at low and high risk of AN, and thus form the basis of individualized screening strategies. However, as correctly pointed out, at present, no literature is available on trends in individuals with f-Hb below the applied cut-off over consecutive screening rounds. More importantly, the intrinsic biological variation of f-Hb in individuals and the variations caused by pre-examination factors such as sample collection, handling and transport, have not yet been investigated with scientific rigour. Such knowledge is a necessary pre-requisite to the interpretation of numerical results (19).

## f-Hb analyses at low concentrations

The study of Grobbee *et al.* (16) explored f-Hb below the cut-off of 10 µg Hb/g faeces and these f-Hb were divided into six categories; 0, >0–2, ≥2–4, ≥4–6, ≥6–8 and ≥8–10 µg Hb/g faeces. Indeed, it now seems very common for academic researchers to explore f-Hb in integer steps from 0 µg Hb/g faeces upwards and some even use significant figures after the decimal point, a less than objective way to report data given the many intrinsic sources of variation in obtaining an examination result. It was stated that the two FIT analytical systems used, the OC-Sensor (Eiken Chemical Co. Ltd, Tokyo, Japan) and FOB-Gold (Sentifit270, Sentinel SCH. SpA, Milan, Italy) perform equally over the relevant concentration range. However, as per their previous work, the examination performance characteristics are, in the view of this author, not documented adequately (20) and the FITTER guidelines of the Expert Working Group on FITs for Screening, Colorectal Cancer Screening Committee, World Endoscopy Organization (21), were not nearly fulfilled. Very importantly, it was stated that the "analytical working ranges for the OC sensor µ and Sentifit270 were respectively 1–200 µg Hb/g faeces and 1–170 µg Hb/g faeces": in fact, these are not correct and enquiries by the author of this editorial to the respective manufacturers confirmed these to be 10–200 µg Hb/g faeces and 3–136 µg Hb/g faeces. Thus, it is germane to ask whether it is acceptable for any work on f-Hb to use numerical data below the lower f-Hb quoted in the Instructions for Use published by the manufacturer of the FIT system used.

## Proposals to improve application of low f-Hb concentrations

It is highly likely that there is wide misunderstanding of the metrological aspects of analysis of f-Hb at low concentrations and this is understandable given the "Tower of Babel" of current terms used for the lowest concentration that can be determined. Moreover, there are a number of somewhat conflicting guidelines and recommendations from professional and governmental bodies, which does not aid clarity. However, since f-Hb is best analysed in medical laboratories accredited to ISO 15189 (22), it is suggested that the recommendations proposed by the Clinical and Laboratory Standards Institute (CLSI), supported by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (23), should be applied. These are very simple to understand and use in practice.

The limit of blank (LoB) is the highest apparent measurand concentration expected to be found when replicates of a blank sample containing no measurand are tested. The limit of detection (LoD) is the lowest measurand concentration likely to be reliably distinguished from the LoB and at which detection is feasible. The limit of quantitation (LoQ) is the lowest concentration at which the measurand can not only be reliably detected, but at which some pre-defined goals for examination bias and imprecision are met. It is vital to note that the LoQ requires definition of analytical performance specifications, which can be set using a number of strategies as documented by the European Federation of Clinical Chemistry and Laboratory Medicine (24) but have not yet been explored for determinations of f-Hb. Often, the analytical performance specification for imprecision adopted for determination of LoQ is coefficient of variation (CV) <5% and, in view of the currently attained state of the art of f-Hb analysis, this might be at least an interim strategy to facilitate the very much needed progress. Bias should be negligible and this requires fully traceable assignment of f-Hb to calibrators.

It may be that there are differences between academic research and the routine reporting of valid numerical results in laboratory medicine. A proposal documented here for the first time is that the LoD could be used in the academic research setting in order to obtain data that could impact on the future use of f-Hb in real clinical practice, while the LoQ is the lowest f-Hb that can be reported by ISO 15189 accredited medical laboratories and all data with lower f-Hb should be reported as less than the LoQ. This proposal requires wide promulgation and discussion and debate, perhaps through the Expert Working Group on FITs for Screening, Colorectal Cancer Screening Committee, World Endoscopy Organization (the academic community) and

 

through the very recently set up IFCC Scientific Division Working Group on Fecal Immunochemical Testing (WG-FIT) (the laboratory medicine community). In any case, a necessary prerequisite at this time is that all involved in generation and application of f-Hb, namely, FIT analytical system manufacturers and suppliers, academic researchers, research funding bodies, authors and reviewers of papers, reviews and material in modern media, journal editors, and professionals in laboratory medicine all use one vocabulary and approaches, those of the CLSI recommendations (23). It is particularly important that manufactures and suppliers document the examination performance characteristics at low f-Hb and use the recommended methodology to provide data on LoB and LoD and also provide high quality precision profiles to calculate LoQ, particularly when desirable analytical performance specifications have been defined more objectively.

Finally, in view of the interest and undoubted value of the determination of low f-Hb, particularly since the dogma that has existed for decades is that "everyone has blood in their faeces", it may be that development of a f-Hb analytical technique with lower LoB, LoD and LoQ than currently available methods would open up further potential for research, initially, and then application in real clinical practice should very low f-Hb examinations prove of value.

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*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Ferlay J, Soerjomataram II, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2016;315:2564-75.
3. Garborg K, Holme Ø, Løberg M, et al. Current status of screening for colorectal cancer. Ann Oncol 2013;24:1963-72.
4. Young GP, Symonds EL, Allison JE, et al. Advances in fecal occult blood tests: the FIT revolution. Dig Dis Sci 2015;60:609-22.
5. Allison JE, Fraser CG, Halloran SP, et al. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver 2014;8:117-30.
6. Fraser CG. A future for faecal haemoglobin measurements in the medical laboratory. Ann Clin Biochem 2012;49:518-26.
7. Fraser CG, Rubeca T, Rapi S, et al. Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. Clin Chem Lab Med 2014;52:1211-6.
8. Symonds EL, Osborne JM, Cole SR, et al. Factors affecting faecal immunochemical test positive rates: demographic, pathological, behavioural and environmental variables. J Med Screen 2015;22:187-93.
9. Digby J, McDonald PJ, Strachan JA, et al. Deprivation and faecal haemoglobin: implications for bowel cancer screening. J Med Screen 2014;21:95-7.
10. Digby J, Fraser CG, Carey FA, et al. Faecal haemoglobin concentration is related to severity of colorectal neoplasia. J Clin Pathol 2013;66:415-9.

 

11. Chen LS, Yen AM, Chiu SY, et al. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncol 2011;12:551-8.
12. Yen AM, Chen SL, Chiu SY, et al. A new insight into fecal haemoglobin concentration-dependent predictor for colorectal neoplasia. Int J Cancer 2014;135:1203-12.
13. Digby J, Fraser CG, Carey FA, et al. Faecal haemoglobin concentration is related to detection of advanced colorectal neoplasia in the next screening round. J Med Screen 2017;24:62-8.
14. Cooper JA, Moss SM, Smith S, et al. FIT for the future: a case for risk-based colorectal cancer screening using the faecal immunochemical test. Colorectal Dis 2016;18:650-3.
15. Ma GK, Ladabaum U. Personalizing colorectal cancer screening: a systematic review of models to predict risk of colorectal neoplasia. Clin Gastroenterol Hepatol 2014;12:1624-34.e1.
16. Grobbee EJ, Schreuders EH, Hansen BE, et al. Association between concentrations of hemoglobin determined by fecal immunochemical tests and long-term development of advanced colorectal neoplasia. Gastroenterology 2017. [Epub ahead of print].
17. McDonald PJ, Strachan JA, Digby J, et al. Faecal haemoglobin concentrations by gender and age: implications for population-based screening for colorectal cancer. Clin Chem Lab Med 2011;50:935-40.
18. Cubiella J, Digby J, Rodríguez-Alonso L, et al. The fecal hemoglobin concentration, age and sex test score: Development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients. Int J Cancer 2017;140:2201-11.
19. Fraser CG. Biological variation: a rapidly evolving aspect of laboratory medicine. J Lab Precis Med 2017;2:35.
20. Fraser CG. Comparison of quantitative faecal immunochemical tests for haemoglobin (FIT) for asymptomatic population screening. Transl Cancer Res 2016;5:S916-S9.
21. Fraser CG, Allison JE, Young GP, et al. Improving the reporting of evaluations of faecal immunochemical tests for haemoglobin: the FITTER standard and checklist. Eur J Cancer Prev 2015;24:24-6.
22. ISO 15189:2012. Medical laboratories -- Requirements for quality and competence. Available online: http://www.iso.org/iso/catalogue_detail?csnumber=56115
23. Clinical and Laboratory Standards Institute. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures, 2nd Edition, Approved Guideline. Wayne, PA, USA: CLSI; CLSI document EP17-A2. 2012. Available online: https://clsi.org/standards/products/method-evaluation/documents/ep17/
24. Sandberg S, Fraser CG, Horvath AR, et al. Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2015;53:833-5.

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