

Faecal Haemoglobin: Newer Approaches to Screening and Diagnosis of Colorectal Disease

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The FIT-based Paradigm for Detection of Colorectal Disease



Screening the **asymptomatic** for colorectal cancer



f-Hb by FIT

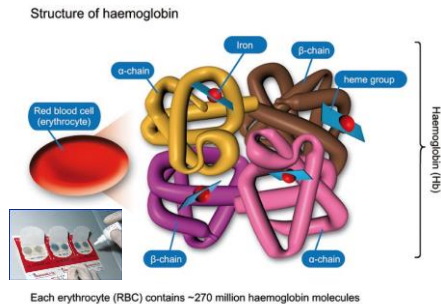


Colonoscopy



Triage of **patients with symptoms** in primary care

Tests for Blood - Haemoglobin - Haem & Globin



Faecal Immunochemical Tests

- Detect intact haemoglobin (and early degradation products) with antibodies (generally polyclonal) to globin.
- Generally easier to collect - one sample only – with user friendly specimen collection devices.
- No dietary interferences.
- Aspirin and anti-coagulants – beneficial.
- More specific for lower GI lesions.
- Generally more analytically sensitive than traditional gFOBT.
- Now advocated in many publications and recommended in most modern guidelines for **asymptomatic population screening** and in recent guidelines on **triage of patients presenting in primary care with lower bowel symptoms**.



Faecal Immunochemical Tests

1. **Qualitative** - positive/negative – analysis done with immunochromatographic test cassettes or strips.



“Cut-off” faecal haemoglobin concentration (f-Hb) for further investigation, usually colonoscopy, set by manufacturer. C₅₀ very different. Not so easy to use! Time dependent reading. Good visual acuity needed. Lot to lot variation.

2. **Quantitative** - measure f-Hb – usually automated immunoturbidimetry - some ELISA, some immunochromatography.

A major advantage, stated very frequently, is that the **cut-off f-Hb for screening** can be set by user.

Quantitative FIT

A number of “closed” analytical systems available – and spectrum growing all the time with new releases.



Calibrators and reagents (FOB Gold) are available that may be used in many “open” analytical systems.

f-Hb concentration data obtained - can we use better in screening and diagnosis?

FIT in Practice: Two Settings

FIT are now widely used for asymptomatic screening and also more and more applied in the assessment of patients presenting with lower abdominal symptoms.

FIT provide one test but in two very different clinical settings .

These settings have different

- aims
- target populations
- interpretations of results
- potential harms
- additional benefits
- f-Hb cut-offs



FIT in Screening



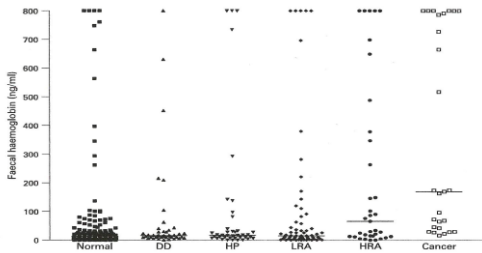
To identify - in an age range selected asymptomatic population - those who are **most likely** to have colorectal neoplasia and would benefit from colonoscopy.
Rule-in Investigation



A "positive" result means that an increased risk of CRC is present in that participant and further investigation is warranted.

A "negative" result means the participant should be re-invited after the screening interval, currently one or two years in different countries.

Faecal Haemoglobin in Health and Disease



Fraser CG, et al. Gut 2008;57:1256-60

f-Hb is Related to Severity of Colorectal Neoplastic Disease

- Median f-Hb concentration was higher in those with cancer than those with no or non-neoplastic pathology.
- Polyp cancers had lower concentrations than more advanced stage cancers.
- Higher f-Hb was also found in those with HRA than with LRA, large (>10 mm) compared with small adenoma, and also in adenoma displaying high-grade dysplasia compared with low-grade dysplasia.

Digby J, et al. J Clin Pathol 2013;66:415-9.

Haemoglobin in Faeces



Normal → Low risk adenoma → Higher risk adenoma → Cancer

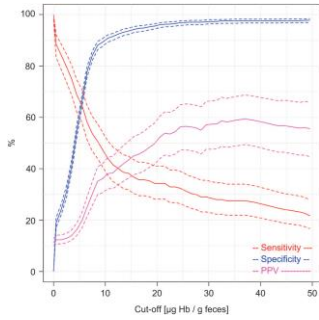
Faecal Haemoglobin →

FIT at Different Cut-off Concentrations

µg Hb/g faeces	Positivity (%)	Detection Rate (%) AN	PPV (%) AN	Specificity (%) AN
10	8.1	3.2	42	95.5
15	5.7	2.7	49	97.2
20	4.8	2.5	53	97.8
25	4.1	2.3	57	98.2
30	4.0	2.3	60	98.4
35	3.6	2.2	63	98.7
40	3.5	2.1	62	98.8

Hol L, et al. Br J Cancer 2009;100:1103-10

FIT at Different Cut-off Concentrations

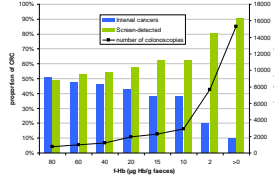


Brenner H and Werner S. et al. *Clin Trans Gastroenterol* 2017;8:e111

Interval Cancers in Scotland

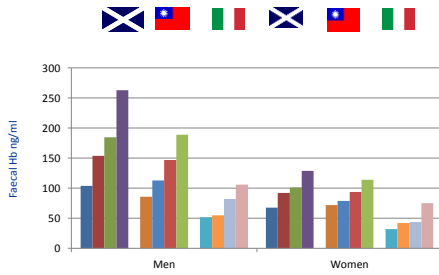


Cut-off (µg/g)	All		Men		Women	
	Screen-detected %	Interval cancers %	Screen-detected %	Interval cancers %	Screen-detected %	Interval cancers %
80	49.2	50.8	53.1	46.9	44.8	55.2



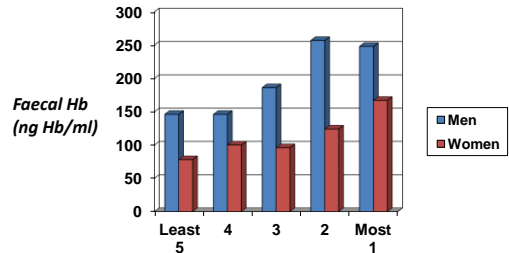
Digby J, et al. *J Med Screen* 2016;23:130-4

f-Hb – Age & Sex – 3 Countries – 50-69 y



Fraser CG, et al. *Clin Chem Lab Med* 2014; 52: 1211-6

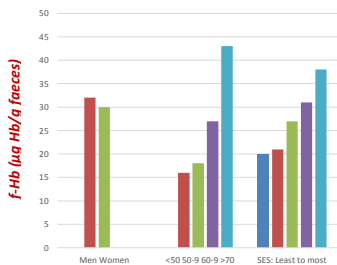
Faecal Hb 95th Percentile and Deprivation – 50-74 y



Scottish Index of Multiple Deprivation quintile

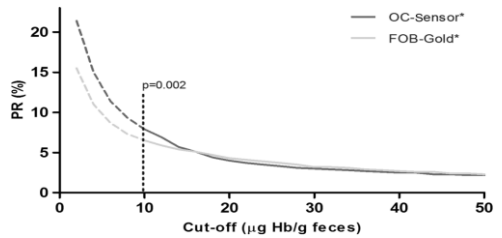
Digby J, et al. *J Med Screen* 2014;21:95-7

f-Hb – by Sex, Age (years) & SES



Symonds EL, et al. *J Med Screen* 2015;22:187-93

Different FIT Systems



*dashed lines represent positivity rates of Hb concentrations under the pre-specified cut-off (10µg Hb/g feces).

Grobbee EJ, et al. *Gut* 2017;66(11):1975-82

FIT (f-Hb) Facts

Faecal haemoglobin concentration is affected by some colorectal disease and

- gender – men have higher f-Hb than women
- age – older people have higher f-Hb than younger
- country – very different – perhaps lifestyle
- deprivation (SES) – more deprived have higher f-Hb than less deprived
- possibly analytical system used (especially at low f-Hb)
- screening round – falls over rounds
- pre-analytical factors

A major current dilemma is: what cut-off or cut-offs should be used in our screening programmes – and how?

Sex Specific Cut-off for Equal Sensitivity for CRC?



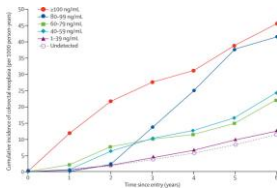
3,022 subjects performed a FIT. At all f-Hb cut-off, sensitivity was higher (range 13-23%) and specificity was lower (range 2-4%) in males compared to females.

ROC curves were similar for both sexes, and equal combinations of sensitivity and specificity could be achieved by adjusting the cut-off.

Equal test characteristics can be achieved by allowing separate cut-offs for both sexes.

van Turenhout ST, et al. BMC Gastroenterology 2014;14:217

Faecal Haemoglobin and Risk



- f-Hb predicts subsequent risk of incident colorectal neoplasia.
- Risk stratification based on f-Hb could help decide priority for colonoscopy and screening interval.

Chen L-S, et al. Lancet Oncology 2011;12: 551-8

Faecal Haemoglobin and Risk



- Data collected from 9561 average-risk subjects (50–74 y) in 4 rounds of FIT screening.
- After 8 years, participants with baseline f-Hb of 8–10 µg Hb/g faeces had a higher cumulative incidence of advanced neoplasia (33%) than participants with 0 µg Hb/g faeces (5%).
- Participants with 2 consecutive f-Hb of 8 µg Hb/g faeces had a 14-fold increase in risk of advanced neoplasia compared to participants with 2 consecutive f-Hb of 0 µg Hb/g faeces.

Grobbée EJ, et al. Gastroenterology 2017;153(5):1251-9.

Risk Scoring

- Many factors influence risk of cancer. The most commonly used risk factors are age, sex, family history, a measure of obesity and smoking.
- “Risk scoring systems which combine f-Hb with risk factor assessment have been shown to improve the sensitivity of the test.”
- “This individualized approach to screening could enable those at greatest risk to be referred for colonoscopy, optimizing resource use and ultimately patient outcomes.”

Cooper JA, 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.

Auge JM, et al. Risk stratification for advanced colorectal neoplasia according to f-Hb in a CRC screening program. Gastroenterol 2014;147:628-36.



		Women	Women	Men	Men
Age (years)		50-69	60-69	50-69	60-69
f-Hb	20-32 µg/g	Low	Low	Average	Average
f-Hb	33-64 µg/g	Low	Low	Average	Average
f-Hb	65-177 µg/g	Average	Average	High	High
f-Hb	>177 µg/g	Average	Average	High	High

FIT for Screening - Future Challenges

- Continue to use one only f-Hb cut-off based simply on colonoscopy resource available?
- Use different f-Hb cut-off concentrations particularly for men and women and possibly for young and old?
- Report "risk" – from f-Hb alone?
- Use more sophisticated data analysis - add age and sex - or add other factors such as deprivation - to create a "risk score"?
- Treat people as individuals? Keep records of individual's f-Hb and consider changes over time? Velocity?

Some difficult to implement - more research needed.



Lower Bowel Symptoms in Primary Care

Lower bowel complaints are common in primary care.

Significant colorectal disease (SCD) is "rare".

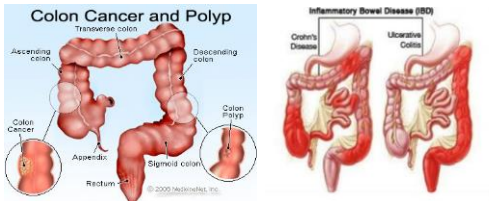
Symptoms of significant colorectal disease overlap with those in benign and functional bowel disorders.

Diagnostic challenge in primary care.

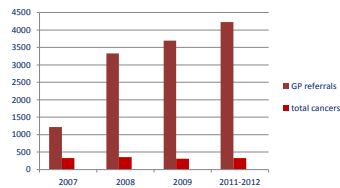
Fear of missing serious disease - many referrals for colonoscopy. Colonoscopy is invasive, costly and a scarce resource.

Significant Bowel Disease

Colorectal (bowel) cancer and adenomatous polyps (higher-risk) and inflammatory bowel disease (IBD – CD and UC).



The Problem



2014 – 4% CRC and 5% IBD



Symptoms are poor predictors of underlying pathology. Vega P, et al. World J Gastrointest Oncol 2015;7:422-33.

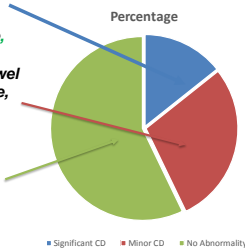
The Rule of Sixths

1/6 have significant colorectal disease (colorectal cancer, advanced adenoma and inflammatory bowel disease,

2/6 have less significant bowel disease (diverticular disease, haemorrhoids, hyperplastic and small polyps, etc) and

3/6 have no detectable abnormality on endoscopy.

Need to find the 1/6 who would benefit most!



<https://scpnblog.wordpress.com/2015/06/12/investigating-bowel-symptoms-remember-the-rule-of-sixths/>

Traditional View of "FOBT" in Assessment of the Symptomatic

NHS NICE CG27

...no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended....

Guideline 67

..... faecal occult blood testing is too insensitive to be used in guiding investigation of symptomatic patients.

BSG

Faecal occult blood testing is of no benefit in the investigation of IDA.



Suspected cancer: recognition and referral - NICE Guideline Published: 23 June 2015

- <https://www.nice.org.uk/guidance/ng12>  National Institute for Health and Clinical Excellence

Cancers of the Lower Gastrointestinal Tract

Very detailed and prescriptive regarding age and symptoms.

- 1.3.1 Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if..... A,B, C and
- tests show **occult blood in their faeces** (see 1.3.4 for who should be offered a test for occult blood in faeces) [new 2015].

f-Hb in Assessment of Patients

NICE: Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. Diagnostics Guidance [DG30]. Published : July 2017.

1.1quantitative FIT are recommended for adoption in primary care to guide referral for suspected colorectal cancer.....

1.2 Results should be reported using a threshold of: **10 µg Hb/g faeces**

NG12 modified - 1.3.4 "stood down"!

Consequences of NG12

- Considerable negativity about use of traditional tests for occult blood in faeces (gFOBT) - but growing realisation that good evidence accumulated that **Faecal Immunochemical Tests for haemoglobin (FIT)** are useful for assessment of patients presenting in primary care with lower abdominal symptoms.
- NICE – Diagnostic Advisory Committee - **Faecal immunochemical tests to triage low risk populations for suspected colorectal cancer referrals in primary care.**

Marie Westwood, et al.

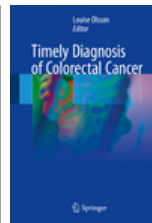
Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and cost-effectiveness analysis.

HEALTH TECHNOLOGY ASSESSMENT
VOLUME 21 ISSUE 33 MAY 2017 – "open"

Marie Westwood, Shona Lang 1, Nigel Armstrong, Sietze van Turenhout, Joaquin Cubiella, Lisa Sirik, Isaac Corro Ramos, Marianne Luyendijk, Remziye Zaim, Jos Kleijn and Callum G. Fraser

Faecal immunochemical tests (FIT) can help to rule out colorectal cancer in patients presenting in primary care with lower abdominal symptoms: a systematic review conducted to inform new NICE DG30 diagnostic guidance.

BMC Med 2017;15:189 – "open"



FITS - Materials and Methods

Study population:

Faecal Hb concentrations were measured on single samples from patients referred for LGI endoscopy from primary care in NHS Tayside,



Index test:

Quantitative FIT on OC-Sensor, Eiken Chemical Co, Japan.



Reference standard:

Endoscopy with histology if needed

McDonald PJ, et al. Colorectal Dis 2013;15:e151-9

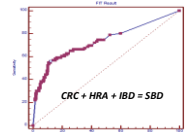
FITS - Study Findings

From 739 invited patients, FIT and endoscopy were completed by 280 (median age: 63 years, 59.6% female) - median time between FIT and endoscopy of 9 days.

6 (2.1%) cancer
23 (8.2%) HRA
26 (9.3%) IBD
31 (11.1%) LRA

194 (69.3%) other (110) and normal (84)

cancer: >1000 ng Hb/mL all adenoma: 59 ng Hb/mL
IBD: 75 ng Hb/mL others and normal: 2 ng Hb/mL



FITS - Study Conclusions

Using a cut-off faecal Hb concentration of 10 µg Hb/g faeces, negative predictive values (NPV) of 100.0%, 94.4%, 93.9% and 93.4% were found for CRC, HRA, IBD and LRA.

In this setting, with high NPV, a negative test result provides considerable reassurance that the patient is unlikely to have significant bowel disease.

FIT provide a good rule-out test and could contribute to reducing unnecessary endoscopy, either alone, or perhaps by incorporation in "risk scoring" systems.

ORIGINAL ARTICLE

Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms

Craig Mowat,¹ Jayne Digby,² Judith A Strachan,³ Robyn Wilson,³ Francis A Carey,⁴ Callum G Fraser,² Robert J C Steele⁴

Gut 2016;65:1463-9

- 750 patients with colonoscopy and f-Hb
- 41.7% patients had undetectable f-Hb
- Test performance assessed for prediction of SBD

	SBD	No SBD	Total
Test +	90	347	437
Test -	12	301	313
Total	102	648	750

PPV = 20.6% NPV = 96.2%
Sensitivity = 88.2% Specificity = 46.4%

FIT in Assessment of the Symptomatic



To assist in deciding - in patients, of any age, presenting in primary care with lower abdominal symptoms – those who would be unlikely to benefit from referral to secondary care for colonoscopy.
Rule-out Test.



A "negative" result means there is considerable reassurance that significant bowel disease (CRC + HRA + IBD) is not present.

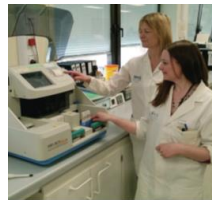
A "positive" result means that the patient may warrant further investigation.

Routine Use of FIT in the Symptomatic

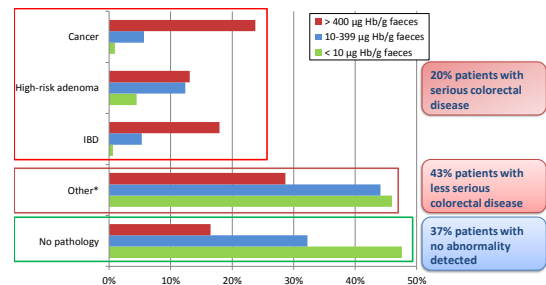
- FIT kits distributed to all primary care surgeries in NHS Tayside.
- FIT analysed daily; HM-JACKarc (Kyowa Medex Co., Ltd.)
- f-Hb reported back electronically to GP with a signposting link for further guidance.
- All FITs received were record-linked with subsequent referrals and colonoscopy reports.
- Quarterly newsletter distributed to GPs with interim analyses on FIT test performance.

Use of FIT in Symptomatic Patients

- FIT introduced as part of the referral process -2/3 referrals now accompanied by FIT.
- 1st year of data: 1,379 patients with FIT completed colonoscopy:
 - 54.4% ≥ 10 µg Hb/g faeces
 - 5.2% > 400 µg Hb/g faeces
- 279 cases of significant bowel disease (SBD) = colorectal cancer + higher risk adenoma + IBD.



Clinical Outcomes

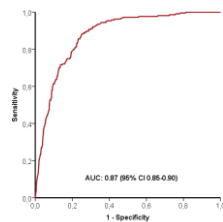


Conclusions and Ramifications

- FIT can be introduced into routine clinical practice
- FIT + clinical assessment + full blood count surpasses the predictive value of symptoms alone, as does f-Hb alone (*Ann Clin Biochem* 2017, June 29, early on-line).
- Using a cut-off of f-Hb < 10 µg/g, in the absence of iron deficient anaemia or persistent diarrhoea, FIT provides an objective means of identifying patients with an extremely low risk of underlying SBD.
- Referrals to secondary care can be reduced.
- At colonoscopy, yield of SBD is related to f-Hb at referral, which can help prioritise urgency.

The FAST Score

The **F**aecal Hb, **A**ge and **S**ex **T**est Score



Cubiella J, et al. *Int J Cancer* 2017;140:2201-2211.

- Derivation cohort: COLONPREDICT
- 4 external validation cohorts (3 Scotland, 1 Spain)
- AUC 0.87(95% CI 0.85 – 0.90)

Overall Conclusions

- Asymptomatic population screening has been widely introduced using FIT as the best non-invasive investigation currently available.
- Screening using FIT does reduce the burden of colorectal cancer.
- Better use of the f-Hb generated must be developed, eliminating “the one cut-off fits all” approach.
- There is firm evidence that FIT rules out most significant bowel disease in patients presenting with lower bowel symptoms – although safety netting required.
- The evidence for development of the NICE guideline DG30 supports this use of FIT in triage of the symptomatic.
- Use of FIT might be improved through risk-scoring.

Risk Scoring Approaches to Date

RESEARCH ARTICLE Open Access
 Risk prediction models for colorectal cancer in people with symptoms: a systematic review
 Tom G. S. Williams¹, Joseph Cubiella², Simon J. Giffin³, Fiona M. Webb⁴ and Julie A. Linder-Smyth⁵

- 15 risk models
- 9 in primary care
- 6 in secondary care

- High sensitivity for colorectal cancer (0.90-0.98).
- Area under the ROC curve (AUC) > 0.85.
- Better discrimination when compared with referral guidelines such as NICE and SIGN.
- Only 4/15 models included a positive test for the presence of occult blood in faeces as a risk factor.

Can This be Improved Further?

Patients who had completed FIT and were attending for colonoscopy completed questionnaire with items for:

- symptoms
- medication
- family history
- diet
- smoking
- alcohol
- physical activity + hours spent sitting
- bmi and waist circumference