FIT - A Tale of Two Settings

Callum G Fraser

Centre for Research into Cancer Prevention and Screening

University of Dundee  Scotland
Possible Conflicts of Interest

- Consultant: Kyowa, Tokyo, Japan
- Consultant: Immunostics Inc., Ocean, NJ, USA
- Funding for travel to meetings: Alpha Labs Ltd, Eastleigh, Hants, UK
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
FIT in Practice: Two Settings

FIT are now widely used for asymptomatic screening and also 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
– possible improvements
– f-Hb thresholds - cut-offs
Target Populations

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

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.
Interpretation

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 two years in many countries.

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

A “positive” result means that the patient may warrant further investigation.
Main Clinical Aims and Cut-off f-Hb

To rule-in colorectal neoplasia.

Cut-off f-Hb may be high - depends on strategy of screening programme and available colonoscopy resource.

To rule-out significant colorectal disease.

Cut-off f-Hb MUST be low.
Problem Caused by Different Cut-off f-Hb

• Scotland and many other screening programmes have **high f-Hb cut-off**, mainly because of colonoscopy constraints.

• Use of FIT with **low f-Hb cut-off** is rapidly rolling out for assessment of symptomatic patients.

• Thus, there will be instances when people, who have recently had a “negative” screening result (low risk of CRC), may get a “positive” result in primary care (worthy of further investigation) after reporting symptoms, simply because of the use of different f-Hb cut-offs in the two very dissimilar clinical settings. Confusing?
Cut-off 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.

1.1 ……quantitative 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

10 µg Hb/g faeces is the most studied cut-off and recommended in a number of the peer-reviewed studies published.

Screening – f-Hb cut-offs used range up to 80 µg Hb/g faeces or more!
Potential Solutions to the Different Cut-off f-Hb

• Use different systems so that specimen collection devices are not the same – but that has many downsides, and it would be much better to use one only system for the two purposes throughout a geographical region.

• Manufacturers make range of specimen collection devices – cap and probe colours, label colours, etc.

• Start to use different names – sFIT and dFIT - but is there better possible terminology? Should EWG on F4S or IFCC SD WG - FIT explore and recommend internationally agreed nomenclature?
Potential Solutions to the Different Cut-off f-Hb

Make information for users as different as possible.

sFIT  dFIT
Potential Communication Problems?

NICE DG30 states:

• .......information to explain the different thresholds and their consequences is available for people who have recently participated in bowel cancer screening.

• Information.......should also be made available to people taking part in the bowel screening programme.

• Would this cast doubt on validity of screening programmes with high f-Hb cut-off?

• Would this encourage participants to ask for their “number”?

• Would this encourage people to seek a symptomatic FIT rather than a screening FIT (a better test?)?
What is a “Low” f-Hb?

• More and more, publications on FIT document numerical data on f-Hb from zero. Is this good academic or satisfactory laboratory medicine routine practice?

• Currently a “Tower of Babel” of terms for “low” f-Hb – detectable, undetectable, sensitive, lower limit, limit of detection, detection limit, limit of quantitation – these are NOT synonyms and confusing.

• Need to use correct metrological terminology to describe, and standard approach to determine, the lowest f-Hb that can be reliably measured, published and used – need knowledge of LoB, LoD and LoQ.

• Topic worthy of consideration and promulgation of consensus by EWG on F4S or IFCC SD WG - FIT?
A Modest Proposal

For academic use: Apply Limit of Detection (LoD)

LoD is the lowest analyte concentration likely to be reliably distinguished from the intrinsic analytical “noise”, the signal produced in the absence of analyte, and at which detection is feasible.

For routine clinical use: Apply Limit of Quantitation (LoQ)

LoQ is the lowest concentration at which the analyte can not only be reliably detected, but at which some predefined goals for bias and imprecision (accuracy) are met. Equivalent to “lower limit of the working range”

Analytical performance specifications required - need numerical statement (such as: bias ~ 0% and imprecision: < 5%) – again EWG on F4S or IFCC WG?
Conclusions/Opinions

• FIT are now used in two clinical settings with many different attributes.

• In particular, different f-Hb cut-offs will lead to confusion and difficulties.

• Work is needed on the terminology of FIT and on other strategies to make the different uses as dissimilar as possible.

• Work is needed on strategies to inform participants and patients of the differences to minimise confusion.

• Use of correct nomenclature for the lowest f-Hb that can be used in academic and routine practice is urgently needed, with consistency across manufacturers, suppliers, researchers, reviewers, editors and users.

• Effort must be expended to improve assays at low f-Hb.