How Low Can FIT Go?

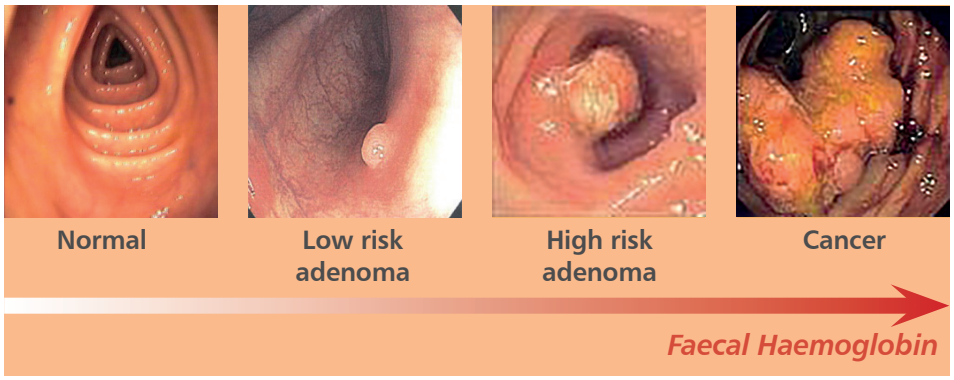
EO expert opinion

Professor Callum G. Fraser Explores the Need for Low Faecal Haemoglobin Concentration Estimates

Faecal immunochemical tests for haemoglobin (FIT) are now widely used in asymptomatic screening for bowel cancer and in assessment of patients presenting with lower bowel symptoms. FIT might also be of value in other clinical settings such as surveillance of patients with previous bowel disease. Quantitative FIT provide estimates of the faecal haemoglobin concentration (f-Hb) for use in all of these.

It is now well documented that the f-Hb is related to the severity of bowel disease. Thus, lowering the f-Hb cut-off used to trigger clinical action confers better detection of bowel cancer, adenoma and other serious bowel pathology. The clinical sensitivity increases, but the positivity rises, the demand for colonoscopy increases, the number of false positive results rises and the positive predictive value falls.

Since a number of users of FIT in assessment of symptomatic patients see cancer detection as the most important role, there is considerable interest in using very low f-Hb as cut-offs. In addition, those wishing to use FIT as a rule-out test to reassure those patients who are unlikely to have significant bowel disease, are also interested in using very low f-Hb cut-offs, so as to minimise the chances of missing disease. So, the question for both approaches, is "how low can FIT go?"



Detectability Characteristics – LoB, LoD and LoQ

This question can only be objectively answered by consideration of what are correctly termed the "detectability characteristics". These are particularly relevant for those examinations, like FIT, that focus on the use of low analyte concentrations.

If samples of faeces which had no haemoglobin present were analysed, a spectrum of results (analytical "signals") would be found. The maximum f-Hb found on analysis of haemoglobin free samples is called the "Limit of Blank", often denoted as the LoB.

The LoB is defined as the highest measured result likely to be observed (typically at 95% probability) for a sample containing no f-Hb (a blank sample).

If samples with very low f-Hb, that is samples with f-Hb slightly higher than the LoB, were analysed, the results (analytical signals) would be generally higher than the LoB.

Now, when these f-Hb results became clearly significantly different from the LoB, the "Limit of Detection", the LoD, has then been exceeded.

The LoD is defined as the lowest f-Hb likely to be reliably distinguishable from the intrinsic analytical "noise", the "signal" produced in the absence of analyte (blank), and at which detection becomes feasible.
LoD is calculated as LoB + 1.645 x SD of samples with low f-Hb.

The factor 1.645 is the "one-sided" number of analytical standard deviations (SD) that gives 95% probability. The LoD will be higher than the LoB.

If samples with f-Hb equal to or higher than the LoD were analysed, the "Limit of Quantitation", the LoQ, might be exceeded.

The LoQ is defined as the lowest f-Hb at which the analyte can not only be reliably detected, but at which some predefined goals for analytical performance are met.

In consequence, this definition means that analytical performance specifications (APS) must be decided before the LoQ can be determined and applied.

Analytical Performance Specifications

The current international consensus is that setting APS can be performed using one of three models:

Model 1:
Based on the effect of examination performance on clinical outcomes:

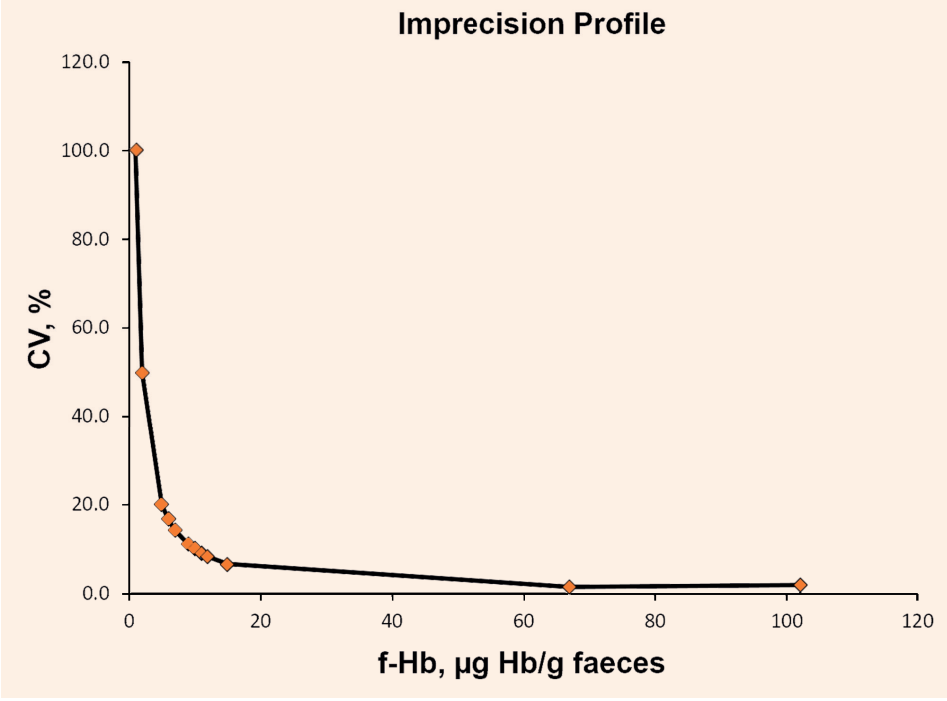
Model 2:
Based on components of biological variation of the measurand:

Model 3:
Based on the state of the art.

At this point in time, data are available only to facilitate a Model 3 approach. It has been proposed that the interim APS for analytical imprecision (and measurement uncertainty) is CV ≤ 10%. This should be lowered when and if FIT technology and methodology improve.

It is vital to note that, while LoB and LoD are basically statistical concepts, LoQ depends on the defined APS. A typical "imprecision profile", in which coefficient of variation (CV, %) is plotted against the f-Hb is shown in Figure 1.

Figure 1. A typical imprecision profile of CV, %, plotted against f-Hb



It can be seen that, if the APS was CV ≤ 10%, the LoQ would be ca. 10 µg Hb/g faeces. However, if the APS was CV ≤ 20%, akin to the now obsolete "functional sensitivity" used many years ago, then the LoQ would be ca. 5 µg Hb/g faeces. So, very importantly, the LoQ depends on the previously decided APS. The LoQ may be equal to or higher than the LoD.

Comparing LoB, LoD and LoQ

One way to think about this difference between LoB, LoD and LoQ is to consider what results would be found if the f-Hb was increased from a starting point of zero – as seen in Figure 2, which shows increasing f-Hb going downwards.

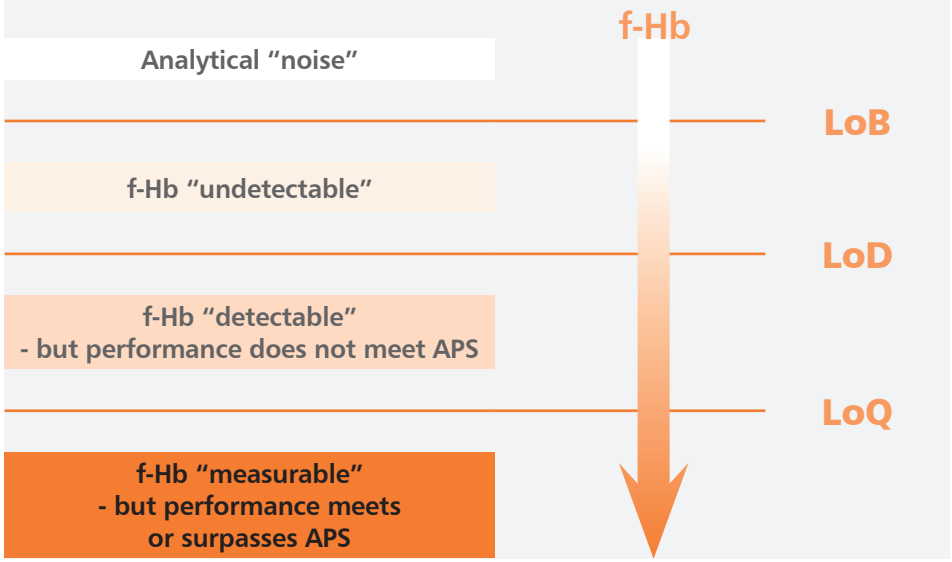
Reporting of Faecal Haemoglobin Concentration Data

Once the LoB, LoD and LoQ have been determined experimentally, or validated, or simply taken verbatim from the literature of the FIT analytical system manufacturer, how should the f-Hb numerical data be reported?

If an accepted guideline is followed, such as that of the National Institute for Health and Care Excellence in NICE DG30, which states that "results should be reported using a threshold of 10 µg Hb/g faeces", reporting should be done using this f-Hb cut-off.

This could be done numerically as < 10 µg Hb/g faeces and ≥ 10 µg Hb/g faeces.

Figure 2. Detectability characteristics and faecal haemoglobin concentration (f-Hb)



Pedantically, using "undetected" for f-Hb < 10 µg Hb/g faeces is incorrect if the LoD is less than this f-Hb, as it is for most FIT analytical systems currently available. Some have suggested simply reporting as a dichotomous approach of positive or negative, but this loses the added value of quantitation that, since f-Hb is related to disease severity, the higher the f-Hb, the greater the likelihood of significant pathology. In any case, if DG30 is followed, the most relevant detectability characteristic is the LoQ, which must be equal to, or ideally less than, the recommended f-Hb cut-off of 10 µg Hb/g faeces.

However, because of the considerable interest in f-Hb lower than the recommended NICE f-Hb cut-off, other reporting strategies might be of more clinical value. The following are suggested:

- f-Hb should only be reported to whole integers,
- f-Hb less than the LoD should be termed "undetectable" or "not detected",
- f-Hb equal to or above the LoD but below the LoQ could be reported as "f-Hb detected",
- for academic use and to inform future developments, f-Hb equal to or greater than the LoD could advantageously be documented numerically in the peer-reviewed literature,
- however, for routine clinical use, numerical f-Hb should be reported only when equal to or greater than the LoQ and
- the following simple reporting system would seem to fulfil current requirements:

f-Hb < LoD - report as: f-Hb not detected
LoD ≤ f-Hb < LoQ – report as: f-Hb detected
f-Hb ≥ LoQ - report the found numerical f-Hb result.

Further Reading

Clinical and Laboratory Standards Institute. Evaluation of detection capability for clinical laboratory measurement procedures, 2nd ed. Approved Guideline. Wayne, PA, USA: CLSI; CLSI document EP17-A2, 2012.

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NICE. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. Diagnostics guidance [DG30]. Published date: July 2017. https://www.nice.org.uk/guidance/dg30