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# Immunochemical Faecal Occult Blood tests

## iFOBTs, FITs

Immunochemical FOBTs exist both as qualitative and quantitative. Qualitative iFOBTs can be visually interpreted. Quantitative tests in turn are often instrument-read and have thus enhanced quality while eliminating the potential for visual bias by the observer [1]. iFOBTs use antibodies to detect the human occult blood [2]. Detecting methods include turbidity, latex agglutination, haemagglutination, colloidal gold agglutination or coloured dye produced by an enzyme. iFOBTs are rapidly replacing gFOBTs because of their many advantages. These include greater clinical and analytical sensitivity [3,4], collection of a single screening sample [5,6-8], simple and hygienic sampling devices [5], higher specificity for lower gastrointestinal tract bleeding [9,10,11], and no dietary restrictions [1,5]. The use of iFOBTs results in improved clinical performance and higher participation rates in screenings [4,12,13]. Compared to gFOBTs, iFOBTs might, however, require a larger initial investment and have slightly weaker sample stability after collection [2,4,14,15,16].

## Sources of bleeding and dietary restrictions

Due to the intraluminal degradation of the Hb moiety globin, iFOBTs specifically detect gastrointestinal bleeding from the lower gastrointestinal tract. Small amounts of bleeding from the upper gastrointestinal tract remain undetected [9,10]. Therefore, it can be stated that iFOBTs have a theoretical advantage over gFOBTs in localising bleeding to the lower gastrointestinal tract [4, 11].

Antibodies that are used in iFOBTs are directed towards human globin epitopes [2]. As globin is species-specific iFOBTs should not be subject to interference from dietary blood [2]. As the potential for dietary interference is small no dietary restrictions are needed prior to or during sampling for iFOBTs [2,5].

## Test performance

Even though iFOBTs are not as widely evaluated as traditional gFOBTs, adequate population-based comparative studies have been made [4]. Overall, the sensitivity of iFOBTs for CRC is stated to be 61–91% and the specificity 91–98% [17]. iFOBTs enable detection of Hb in faeces at lower concentrations than gFOBTs, and therefore increase clinical sensitivity by detecting small or intermittently bleeding lesions [2].

Adequate clinical sensitivity and specificity for screening can be obtained using a single iFOBT test per subject [2, 6, 7]. Likely due to the improved clinical performance, the use of only one or two samples and simpler sample collection and handling techniques [4], screening programmes with iFOBTs has been shown to have a participation rate higher than gFOBTs [12, 13].

Even though gFOBTs are more affordable than iFOBTs, studies have shown that use of iFOBTs is a more cost-effective strategy in CRC screening [18-20]. This is likely due to the increased sensitivity of the tests as well as the higher participation rate [4]. The higher test costs are also balanced by use of automated analysers that lead to reduced staff costs, and by the need of performing fewer tests per patient [2]. Cost-analyses do, however, need to be made separately in each country, as e.g. test and personnel costs, logistics and preferences of screening vary [4].

## Adjustable cut-off concentration

The most prominent advantage of a quantitative FOB test is that the user can select the cut-off concentration in order to decide on further investigation [1]. This means that the analytical sensitivity of the test can be adjusted according to e.g. screening settings, national guidelines or local requirements [1, 3]. The goal with choosing a cut-off concentration is to provide an adequate positivity rate with acceptable trade-off between detection rate and unnecessary colonoscopies performed. The choice depends on the test device, sampling, number of samples used, intended detection rate, prevalence of CRC in population, and political issues such as availability of colonoscopy [2, 21].

Knowing the total amount of Hb in the faecal mass, enables comparison of FOB results obtained with different methods. Test manufacturers use various sampling devices and buffers, collect various masses of faeces and report Hb concentrations in different ways. Therefore FOB results expressed in ng Hb/ml buffer are not comparable between different methods [22]. A suggestion on standardisation of units for reporting faecal Hb concentrations has been made [23]. The only unit that allows comparison of FOB results between test devices and across clinical studies is µg Hb/g faeces. The unit can be calculated if the dilution ratio of the sample is known, but sophisticated automated iFOBTs provide the user with results expressed in µg/g automatically.

## Patient-specific follow-up and screening strategies

Occult bleeding increases gradually with growing size of polyps and advancing stage of CRC, and FOB tests can potentially detect both CRC and its preliminary stages [6, 24, 25]. Qualitative test indicating only that the result is positive, do not give any information on the amount of occult bleeding. Risk stratification based on the exact numerical Hb concentration might help clinicians in identifying subjects with alarmingly high FOB concentrations that should undergo further examinations immediately. The interval between screen-detected disease and the start of definitive management is an unpleasant time for the patient and it presents the opportunity for disease progression [3,26].

Irregular bleeding patterns and rates [27] as well as many other factors might cause varying faecal Hb concentrations. There is a risk of false results in case a qualitative test is used and the subject's average Hb concentration in faeces is very variable and/or close to the cut-off concentration of the FOB test. In these cases a quantitative test would clarify the situation significantly, thus eliminating guess-work, false positives and unnecessary further examinations.

## Further investigations

If a FOB test is positive, an investigation is performed to identify the source of bleeding. The most common techniques for further investigations include colonoscopy, flexible sigmoidoscopy, air-contrast barium enema, molecular markers, virtual colonoscopy or colon capsule endoscopy [5, 11]. Colonoscopy is considered the most effective visualisation technique to detect CRC and high-risk adenomas [4], and the recommended method to evaluate the colon in patients with increased FOB concentrations [11].

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