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Faecal Haemoglobin Examinations Have Come of Age, but Further Maturation Seems Desirable.

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Coming of age is the transition from childhood to adulthood and, traditionally, was considered to be at 21 years. It is now 21 years since the first guaiac faecal occult blood tests (gFOBT), surrogate markers for faecal haemoglobin, were sent to eligible invitees in the UK colorectal cancer screening pilot. (1) Following this and subsequent pilots in England and Scotland, national rollouts began in 2006 and 2007 respectively, followed by programmes in Wales and Northern Ireland. These programmes employed different screening algorithms, but all used gFOBT as the initial investigation. However, the disadvantages of gFOBT were more and more acknowledged as evidence grew concerning the merits of quantitative faecal immunochemical tests (FIT) that gave estimates of faecal haemoglobin concentration (f-Hb). (2) Following evaluations in Scotland (3) and England, (4) FIT were successfully introduced into the screening programmes of the four UK nations, the main benefits being increased uptake and improved detection of colorectal neoplasia. But, further maturation of the screening programmes does seem warranted. The international recommendations are that screening should be offered to 50-74 year olds, (5) but this has not been achieved to date except in Scotland. Throughout the UK, different f-Hb thresholds are used to decide the participants who would most benefit from further investigation, usually colonoscopy. Compared to other countries, these thresholds are at high f-Hb; driving down the f-Hb thresholds used would increase the colorectal cancer (CRC) detection rate (CDR) and would decrease both incidence and mortality through removal of adenoma, potential CRC precursor lesions, but this would require additional endoscopy resources. Currently, one threshold is used for all, but women are disadvantaged by this, since they have lower f-Hb, lower CDR, higher interval cancer proportions, and screening has a

smaller effect on CRC mortality than for men: using different f-Hb thresholds for the sexes to give the same “positivity”, as has been successfully introduced in Sweden and Finland, would be of advantage. (6) It has been shown that, in screening, any detectable f-Hb (i.e., above the limit of detection (LoD)), even if lower than the threshold applied, does confer risk of future neoplasia and the risk is related to the f-Hb. (7) It has been often suggested that screening interval might be linked to the f-Hb and participants with such results could receive different communications and advice depending on the f-Hb; these proposed strategies do not seem to have been translated into practice. Moreover, integration of f-Hb estimates into “risk-scores”, including data on easily obtainable data such as sex, age, and deprivation status, all of which significantly affect f-Hb, (8) and perhaps results of other investigations, has been proposed as likely to lead to improvements. Further, in screening, how f-Hb is used, if simply one of a set of variables used in the assessment of risk, may become increasingly complex if artificial intelligence (AI) and machine learning (ML) techniques become practical. Other aspects also warrant attention, including harmonisation of methods, since FIT systems give different results (9) and dissimilar clinical outcomes at the same f-Hb threshold. (10) This casts some doubt on the transferability of data using different FIT systems. This issue is being addressed by the IFCC SD WG-FIT. (11) FIT-based screening has certainly come of age, but further maturation of the use of the f-Hb generated would have significant advantages for population health.

Since the first small study (12) into the use of f-Hb estimates in the assessment of patients presenting in primary (or secondary) care with lower abdominal symptoms, significant evidence has accrued that f-Hb can be very successfully applied in this

clinical setting. (13) Indeed, this use of FIT became the subject of a National Institute for Health and Care Excellence (NICE) guideline (DG30) which subsequently influenced the update of the important guideline (NG12) on referral of patients from primary to secondary care in England. (14,15) The evidence base at that time was small, although convincing. However, since then, many further studies have been performed, all showing that FIT can be very successfully applied in the triage of patients with symptoms: these are described in detail in a comprehensive recent review. (13) In addition, as a result of the COVID-19 (SARS-CoV-2) pandemic in which endoscopy resources became highly constrained, the use of FIT in assessment and triage of patients became widespread with recommendations as to how to interpret the f-Hb issued, for example, by Scottish Government. (16) In marked contrast to the use of FIT in screening, the DG30 recommended threshold f-Hb to be used for referral was 10 µg Hb/g faeces, but this is controversial: some suggest using the LoD as the threshold, so maximising clinical sensitivity to equal that of colonoscopy. (17) f-Hb concentrations are positively associated with disease severity (18) and during the pandemic, higher f-Hb thresholds were applied to direct the very limited endoscopy resources available to those who were at highest risk and would most benefit. A variety of strategies were developed to cater for those patients with f-Hb greater than 10 µg Hb/g faeces but less than the pandemic-led high f-Hb thresholds. The evidence and the practice have both evolved rapidly so that FIT are not only performed in patients as per NICE DG30 and NG12 guidelines, but also done on all patients presenting with lower bowel symptoms irrespective of age, with the results being interpreted with data on symptoms and other results, particularly the full blood count, giving an extremely useful investigation, not only for CRC but also for other significant bowel disease, usually (although not universally) defined as

CRC plus higher risk adenoma (HRA) plus inflammatory bowel disease (IBD). (19) However, again there are issues still requiring further evaluation. FIT in assessment of patients is not a perfect investigation and CRC can occur, albeit rarely, in those patients with undetectable f-Hb, sometimes termed “FIT-negative CRC”: the approach is to undertake safety-netting, involving follow-up of patients in whom symptoms persist or worsen but there seem to be no widely accepted evidence-based strategies. Further, many guidelines, local and national, suggest a repeat FIT at a range of intervals but there is little evidence on the use of this strategy; further investigation of serial f-Hb results in individuals. is urgently required. (20) Some studies have investigated the improvement of the diagnostic accuracy by including additional biomarkers such as faecal calprotectin, M2-pyuvate kinase and volatile organic compounds in patients with symptoms, but there seems little general uptake of this concept in routine practice. (13) In addition, as for CRC screening, there have been a number of proposals for the use of risk scores adding additional information to the f-Hb and, while interesting concepts, there seem to have been no prospective studies to date. (13) Although in the UK FIT are usually carried out in medical laboratories, point -of-care testing, particularly in secondary care clinics, might have advantages in speeding up the triage of patients with symptoms, as recently demonstrated; (21) such approaches seem very worthy of further study. Additional roles for f-Hb in the care of patients with IBD have been suggested, particularly in the monitoring of mucosal healing and prediction of relapse, but further work seems necessary to identify the optimum roles of FIT in monitoring patients with IBD. (22)

Adenoma are potentially precursor lesions for CRC and, in consequence, polypectomy during colonoscopy does reduce future CRC risk. However, some of

these patients do have an increased risk of developing further polyps and perhaps CRC. Thus, post-polypectomy surveillance is widely undertaken, usually in accord with national guidelines which are regularly updated. As CRC screening has expanded globally, more and more patients have required surveillance and this has put considerable additional pressure on the limited endoscopy resources. It would be of advantage, therefore, to have a simple test such as FIT to direct surveillance to those patients who would most benefit. (13) There is some evidence that that f-Hb could indeed provide an objective estimate of the risk of advanced neoplasia and could enable tailored individual scheduling of colonoscopy. (23) Again, further work is warranted to generate more evidence-based data on how to apply FIT and to whom, such as that recently published. (24)

In all clinical settings, there are individuals who have f-Hb above the threshold applied but who have no detectable pathology on colonoscopy: these are often known as “false positive” results. These are sometimes attributed to upper gastrointestinal bleeding and often to medicines such as anti-coagulants including aspirin, non-steroidal anti-inflammatory drugs, and protein pump inhibitors; on the balance of available evidence, these seem generally irrelevant. In contrast, recent studies have shown that detectable f-Hb is associated with increased all-cause and cause-specific mortality, and with longer-term conditions including diabetes, hypertension, cardiovascular disease, and psoriasis, and with probable intake of particulate matter. (25) All of these conditions are associated with systemic inflammation. In consequence, the suggestion has been made that elevated f-Hb has considerable potential to identify individuals at risk of, or who already suffer from, early stage, undiagnosed, chronic disease. If f-Hb did prove an effective biomarker

for chronic disease, individuals with detectable f-Hb, but without an obvious source of gastrointestinal blood loss, might gain advantage from further assessment and early intervention such as through individual recommendations on modifying lifestyle and perhaps even therapeutic initiation. Further research on this hypothesis seems warranted, possibly using linkage of information from a spectrum of clinical databases.

Finally, in screening using current FIT systems, more than 50% of participants have an undetectable f-Hb.(8) In assessment of patients presenting with symptoms, again many have an undetectable f-Hb; in one study of the use of FIT in routine practice in this clinical setting, 78.1% of patients had f-Hb < 10 μg Hb/g faeces. (26) These findings seem incompatible with the dogma that everyone has blood in their faeces. Whether it be of interest to have a FIT system that had a lower LoD than those currently available seems a germane question. After all, “high sensitivity” analyses of, *inter alia*, thyrotropin, troponins, and C- reactive protein have proven of significant clinical value. However, until this hypothesis was proven and commercial advantages became clear, manufacturers of FIT systems are unlikely to invest in developing such methods. The authors hope that the methodology to investigate “hs-FIT” will be developed and assessed; perhaps imaginative use of current systems could facilitate such research.

Many of the suggested potentials for f-Hb measurements, as described previously in 2012, (27) have ensued; however, there are still many significant unanswered questions for which professionals in laboratory medicine could play a prominent role in solving.

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