

The use of faecal haemoglobin in deciding which patients presenting to primary care require further investigation (and how quickly) – the FIT approach

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ABSTRACT

Patients presenting to general practitioners (GPs) with new bowel symptoms can be difficult to assess since symptoms are poor predictors of pathology. National Institute for Health and Care Excellence referral guidelines highlight features that may suggest colorectal cancer (CRC) including rectal bleeding, palpable mass, iron deficiency anaemia, but also non-specific symptoms such as weight loss. In those patients referred for investigation on the basis of symptoms alone the yield of CRC is low (2-3%). Faecal immunochemical tests (FIT) quantify faecal haemoglobin (f-Hb) and are widely used in bowel screening programmes. A number of groups have now studied the utility of FIT in patients attending primary care with new bowel symptoms. Studies have concluded that if the FIT is negative and clinical assessment and full blood count normal then the risk of underlying significant bowel disease (SBD) is extremely small. Furthermore, patients with f-Hb ≥ 400 $\mu\text{gHb/g}$ faeces have >50% risk of

SBD and should be investigated urgently. Thus, a single f-Hb requested by GPs provides both a reliable prediction of the absence of SBD, and an objective assessment of the need and urgency of further investigation.



Abbreviations (in alphabetical order)

CHI: Community Health Index

CRC: colorectal cancer

FIT: faecal immunochemical test

f-Hb: faecal haemoglobin concentration

GI: gastrointestinal

GP: general practitioner

IBD: inflammatory bowel disease

ICD: International Classification of Diseases

IDA: iron deficiency anaemia

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

SBD: significant bowel disease



INTRODUCTION

Lower gastrointestinal (GI) symptoms are poor predictors of significant bowel disease (SBD), namely colorectal cancer (CRC), inflammatory bowel disease (IBD) or higher risk adenomas (HRA); and cannot be relied upon to differentiate between CRC and non-significant or functional disorders (1). Guidance on the “two week wait” (2WW) for urgent referral for further investigation of patients with symptoms suspicious of cancer was introduced in 2004 in England. There is evidence that this has led to a large increase in referrals, but no change in the overall survival (2). In addition, in a recent five-year national cohort study, patients from primary care practices with the highest urgent suspected cancer referral rates did not have a lower likelihood of late

stage diagnosis than those from practices with lower referral rates (3). There are an increasing number of complex guidelines available to general practitioners (GPs) to try and help with further decision making such as those from the National Institute for Health and Care Excellence (NICE) in England (4,5) and Scottish Government suspected cancer referral guidelines (6), but these are open to interpretation and have serious limitations.

Our local health care system in NHS Tayside, Scotland, serves a population of around 400 000. Each year approximately 4000 patients are referred from primary care for assessment of bowel symptoms via a dedicated referral portal, ensuring equity of access and a streamlined booking process. The percentage of referrals from GPs marked as ‘urgent’ or ‘urgent suspected cancer’ consistently runs at 35–40%. Referrals are triaged by consultant gastroenterologists; 75% are brought straight to investigation such as colonoscopy and the remainder seen in outpatient clinics. Demand for endoscopy services has continued to escalate due to the ageing population and increasing referrals with over 70,000 colonoscopies carried out every year in Scotland (7) with concerns about insufficient workforce to meet demand and increasing waiting lists. Furthermore, colonoscopies are not without issues. When patients undergo colonoscopy to investigate symptoms, the yield of significant bowel disease is low, with local audit revealing CRC in only 2% and IBD in 5%. Furthermore, colonoscopies are not 100% accurate with variations in the number of cancers reported post-colonoscopy by NHS providers in England (8) and there can be adverse patient events such as perforation and bleeding and although these are rare, the effect should not be underestimated (9).

New means of assessing patients in primary care were urgently needed to help GPs determine which patients need rapid investigation and, in turn, ease pressure on secondary care services.

Faecal immunochemical tests (FITs) for haemoglobin (Hb) are specific for intact human Hb and its early degradation products. *Quantitative* FIT, based upon latex agglutination immunoturbidimetry and giving a numerical result for the faecal Hb (f-Hb) concentration have been recommended over *qualitative tests* to remove reader variability, inter-batch variability and to improve the diagnostic accuracy of the test. The use of FIT is already well established in CRC screening programmes worldwide (10-13). There is increasingly compelling evidence that the use of *quantitative* FIT in patients presenting to GPs with new bowel symptoms suggest high specificity and negative predictive values (NPVs) for CRC including our own 6-month pilot study which showed that the negative predictive values of f-Hb for CRC, HRA and IBD were 100%, 97.8% and 98.4%, respectively (14-20). A recent very large study from the NICE FIT Steering Group concluded that in patients referred via the 2WW pathway in England, FIT was superior to symptoms in predicting pathology (21). However there is still lack of awareness and perceived barriers to using FIT as an investigative test in primary care (22) and there is an on-going need for good quality evidence to ensure confidence in the use of FIT in this context with data collation and shared learning required (23).

AIM

The aim of this project was to assess whether the use of FIT by primary care could more efficiently identify patients presenting with new bowel symptoms who required further investigation. In addition, could the use of FIT prevent patients being referred unnecessarily for invasive procedures.

METHODS

In the NHS Tayside Board area, FIT kits (Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo,

Japan, supplied by Alpha Labs Ltd, Eastleigh, Hants, UK) along with patient instruction leaflets, were made available to GP practices beginning in December 2015. GPs were recommended to request fHb to guide referral of patients with any lower GI symptoms. Uniquely combined with electronic test requesting (using Sunquest ICE) of a concomitant 'Colorectal Bundle' of a Full Blood Count and Anaemia Screen along with patient symptoms selected from a drop-down menu, this ensures high uptake of FIT testing and completeness of data. Patients are provided with a pictorial instruction leaflet and requested to return the completed FIT specimen collection device as soon as possible to the GP facility and, from there, the devices are delivered to Blood Sciences, Ninewells Hospital and Medical School, Dundee, at ambient temperature, by the routine sample collection service and, if required, stored at 4°C prior to analysis. Analyses are carried out Monday to Friday; most samples are analysed on the day of receipt. Results are reported electronically to the requesting GP after fHb measurement using one HM-JACKarc (Hitachi Chemical Diagnostics Systems) FIT system which has a limit of detection (LoD) of 2 µg/g, a limit of quantitation (LoQ) of 7 µg/g and an upper measurement limit of 400 µg/g (24). Samples with results above the upper measurement limit are therefore reported as >400 µg/g, and patients with f-Hb ≥ 10 µg/g are defined as worthy of further investigation as recommended in NICE DG30 (5). The reports also sign-post GPs to web-based advice that f-Hb <10 µg/g, in the absence of iron deficiency anaemia (IDA), severe persistent symptoms, or a rectal or abdominal mass, suggests that CRC is extremely unlikely.

Numerical FIT results were retrieved from the laboratory database and linked by means of the Community Health Index (CHI) number with the electronic patient record to access all correspondence, laboratory results, referrals to secondary care, colonoscopy findings, hospital

admissions and attendances at the primary care out-of-hours service. In addition, a *post-hoc* anonymised record linkage with the Scottish Cancer Registry (SCR) was carried out in order to identify any cases of CRC that had been overlooked (International Classification of Diseases [ICD] codes C18, C19 and C20). All cases of CRC were confirmed histologically. Ethical approval was in place to safeguard the record linkage. MedCalc statistical software (MedCalc Software, Mariakerke, Belgium) was employed for calculations. Regular newsletters were emailed to all GPs over the first year of offering the test. To gauge the impact of offering FIT as a routine test, a questionnaire was emailed to all NHS Tayside GPs in 2017 asking various questions about the service, including availability and use of FIT tests and asking for free-text comments.

RESULTS

The FIT service was introduced as a routine test in December 2015, and in the first year of routine use 5422 patients submitted 5660 FIT kits, of which 5372 were analysed (positivity: 22%). 2848 patients were referred immediately to secondary care and 3 with f-Hb <10 µg/g presented acutely within days with obstructing CRC. 1447 completed colonoscopy in whom overall prevalence of SBD was 21% (95 CRC (6.6%), 133 HRA (9.2%) and 68 IBD (4.7%)); in patients with f-Hb <10 µg/g it was 6.6% vs. 32.3% in patients with f-Hb ≥10 µg/g. 2521 patients were not immediately referred (95% had f-Hb <10 µg/g) of which four (0.2%) later developed CRC. Record linkage identified no additional CRC cases within a follow-up period of 23–35 months (25).

EFFECT ON PATIENT SAFETY

In the first year of introducing FIT as a standard test available to GPs, referrals in NHS Tayside from primary care via the Colorectal Pathway fell 9% and referrals to Gastroenterology fell 24%.

The overall reduction in referrals was therefore 15% (25). This was on a background of rising referrals over the last 5 years. This large drop in referrals meant that around 1000 patients were not referred in a 12 month period who would otherwise have been placed on the colonoscopy waiting list had FIT not been available to their GPs. For these patients, the availability of FIT meant that they did not have to undergo unnecessary colonoscopy.

Our approach has been well received within the local primary care community. 98% of the 179 GPs surveyed said that they had requested a FIT with 98% happy with the turnaround time of the result. GPs benefit from having quantitative results rapidly available along with clinical acumen to aid decision making. GPs and patients can therefore have a more informed discussion about further investigation with 32% of GPs stating that FIT testing always helps assess the risk of significant pathology and 63% saying that it helps most of the time. Using a FIT test appears very acceptable with a high rate of patient compliance – this is evident with over 70% of referrals including a FIT result with GPs reporting that when offered, 32% of patients are always willing to complete the test and 67.6% willing most of the time to complete a test.

Patients with a low FIT can be reassured that nothing immediate needs to be done, decreasing anxiety in this group while those with high results have, in many cases, led to more rapid investigations.

PATIENT DIAGNOSIS

For an individual patient, the impact is extremely significant. Firstly, a negative FIT test in the absence of other worrying signs/symptoms means that they are highly unlikely to have significant bowel disease. This means that they do not need an invasive and unpleasant colonoscopy and can be reassured that they do not have significant

disease thus reducing anxiety and a wait for further tests. For patients with on-going symptoms, advice and safety netting is available with repeat FIT testing if necessary. For patients with elevated FIT results, they may well be 'fast-tracked' to a more urgent investigations thus leading to a quicker diagnosis of significant bowel disease.

During the first year of FIT, analysis showed that at the vetting stage, 242 patients had the urgency of their referral altered by the consultant gastroenterologist prior to colonic investigation: 166 referrals were upgraded on the basis of the f-Hb $\geq 10 \mu\text{g/g}$ in which the yield of SBD was 33.7% (17 Colorectal Cancer, 14 Inflammatory Bowel Disease and 25 High Risk Adenomas). Forty-four patients had their referral downgraded based on f-Hb $< 10 \mu\text{g/g}$ from either 'urgent' or 'urgent suspected cancer' to 'routine'; only two of these patients had SBD (both HRA). Thirty-two patients who had f-Hb $< 10 \mu\text{g/g}$ were upgraded on the basis of symptoms and patient history only; three had HRA and one patient had IBD.

For individual patients and the vetting consultants, the ability to upgrade or downgrade referrals on the basis of the FIT result is very significant. Before the availability of FIT, symptoms were the main determinant of urgency of referral so knowledge of the FIT result is now integral to the vetting process. Our experience shows that upgraded referrals made on the basis of the FIT result, results in faster diagnosis of significant diseases in these patients. In contrast, downgrading does not significantly delay a diagnosis.

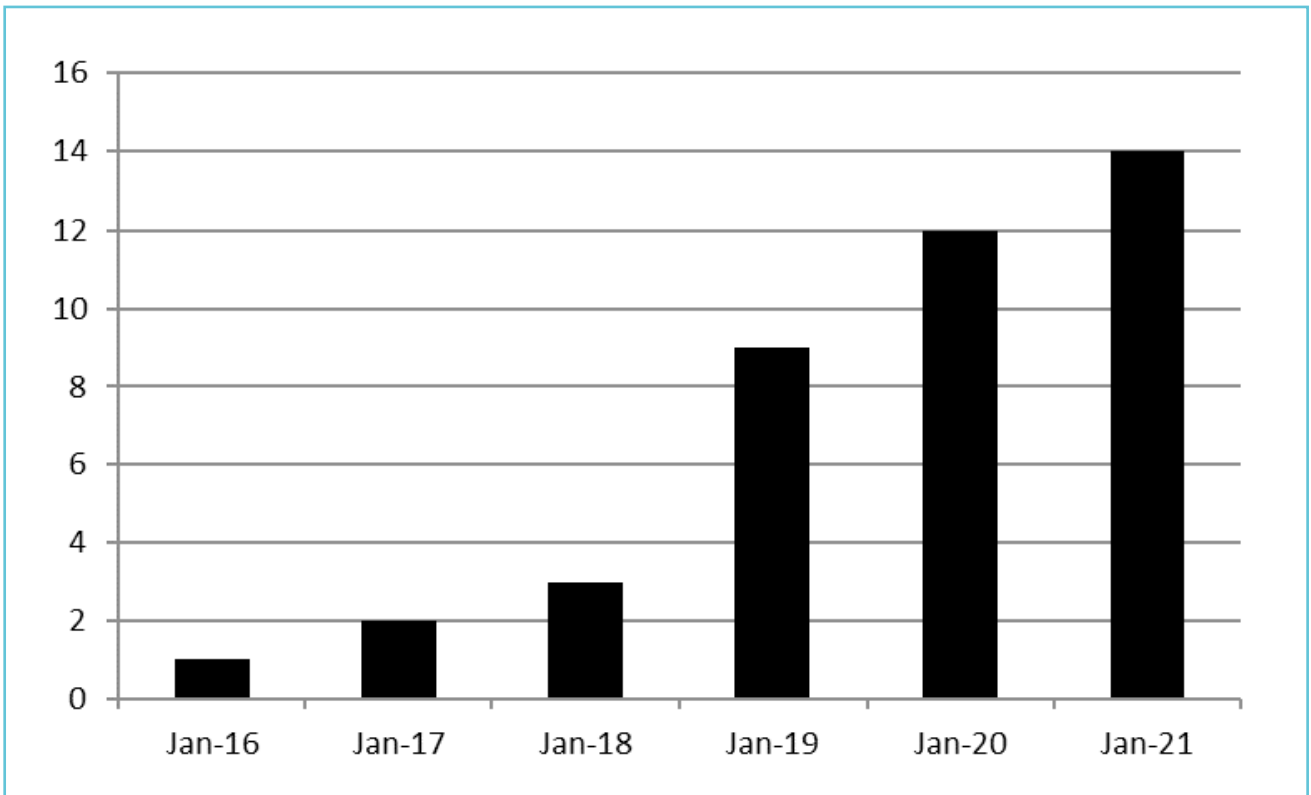
EFFECT ON OTHER HEALTH BOARDS

The roll out of FIT to all 14 Health Boards in Scotland has been accomplished over the last five years (Figure 1). This was initially via the creation of a Short Life Working Group and position statement in 2017 then facilitated with two key stakeholder meetings in 2018 and 2019 leading to collaborative working across Health Boards

both in terms of clinical approach and also laboratory processes.

The roll out of FIT across Scotland over the last five years has been of great benefit to laboratory colleagues across the country enabling more direct dialogue with other laboratories. Smaller laboratories can often feel quite isolated and the work undertaken to roll out FIT requesting has enabled them to be part of a national initiative. To date, there are four Health Boards performing their own FIT analysis using the same HM-JACKarc analytical platform, with the others sending kits on a daily basis to Tayside thus ensuring that there is rapid testing and reporting across the country. A common patient instruction leaflet has been widely used across the Health Boards, based on the Tayside version. NHS Tayside was a very early adopter in Scotland of NPEx software (an IT product to connect all UK labs through a single exchange hub) and our expertise and experience of this has greatly helped the roll out of FIT across the country. Where possible, electronic requesting of FIT from primary care has been encouraged. This work illustrates how diagnostic tests can be used effectively in clinical pathways and the interaction of clinicians and laboratory staff has led to the sharing of ideas, collaboration and interaction between all Health Boards in Scotland setting up this service. The service development has also in some cases led to technological changes in some boards too, with the introduction of NPEx to manage effective sample flow of referral tests between boards.

For clinicians across Scotland, the pioneering work undertaken by the laboratory and clinical team in Tayside has been transformative in improving diagnostic pathways for colorectal symptoms and the Tayside approach on the use of FIT has been adopted for local use with great enthusiasm and the benefits are now being seen in many areas. It has had the added benefit of more standardised requesting and referrals nationally.

Figure 1 Number of NHS Scotland Health Boards offering FIT by year

WIDER EFFECTS

Due to Tayside's pioneering work, FIT testing in primary care is now universally available in NHS Scotland. The service was in place pre-COVID, but its value to diagnostic services has been greatly emphasised during the recovery phase of COVID. Indeed, national consensus has been achieved on pathways and FIT thresholds for use in COVID service recovery as a direct consequence of the group's work (26). Furthermore, high risk patients (based on FIT ≥ 400 ug/g) have been prioritised for colonoscopy first. FIT has now been included in referral protocols by the Association of Coloproctology of GB and Ireland and has been incorporated into the new Colon Capsule Endoscopy (CCE) programme, allowing clinicians to triage low risk (based on FIT levels) patients to CCE.

The universal adoption of FIT along with associated clinical cut-off points and investigation

protocols across Scotland has had a significant impact on the investigation of patients presenting to primary care with new bowel symptoms across the whole country. It has meant equality of access for patients regardless of geography to diagnostic tests based on an objective measure (i.e. a FIT result) along with clinical assessment rather than on symptoms alone. Laboratory data and clinical outcomes have been shared for learning and future planning between the Scottish Health Boards. This has, in turn, led to the combining of data from three boards thus adding to the evidence for the use of FIT (27). This collaboration has also led to a consensus paper on the use of FIT as part of a national recovery strategy for colonoscopy services in symptomatic patients during the Covid-19 pandemic (26). Figure 2 shows the number of FIT tests analysed by Tayside over the last year. Following a marked reduction during the first wave of the COVID-19

pandemic, there has been a sharp increase in FIT requests since the guidance was published in early July 2020.

This common approach is very rare outside national bowel screening programmes and has been encouraged and supported by Scottish Government who has recognised the benefits for service delivery and patients.

SUMMARY

To our knowledge, we are the first area in the United Kingdom to introduce daily FIT testing to Primary Care for ALL age ranges and with ANY new bowel symptoms as an adjunct to clinical judgement and as an integral part of the colorectal referral pathway. Results are reported electronically back to GPs with signposting to local clinical advice and suggesting urgent referral if

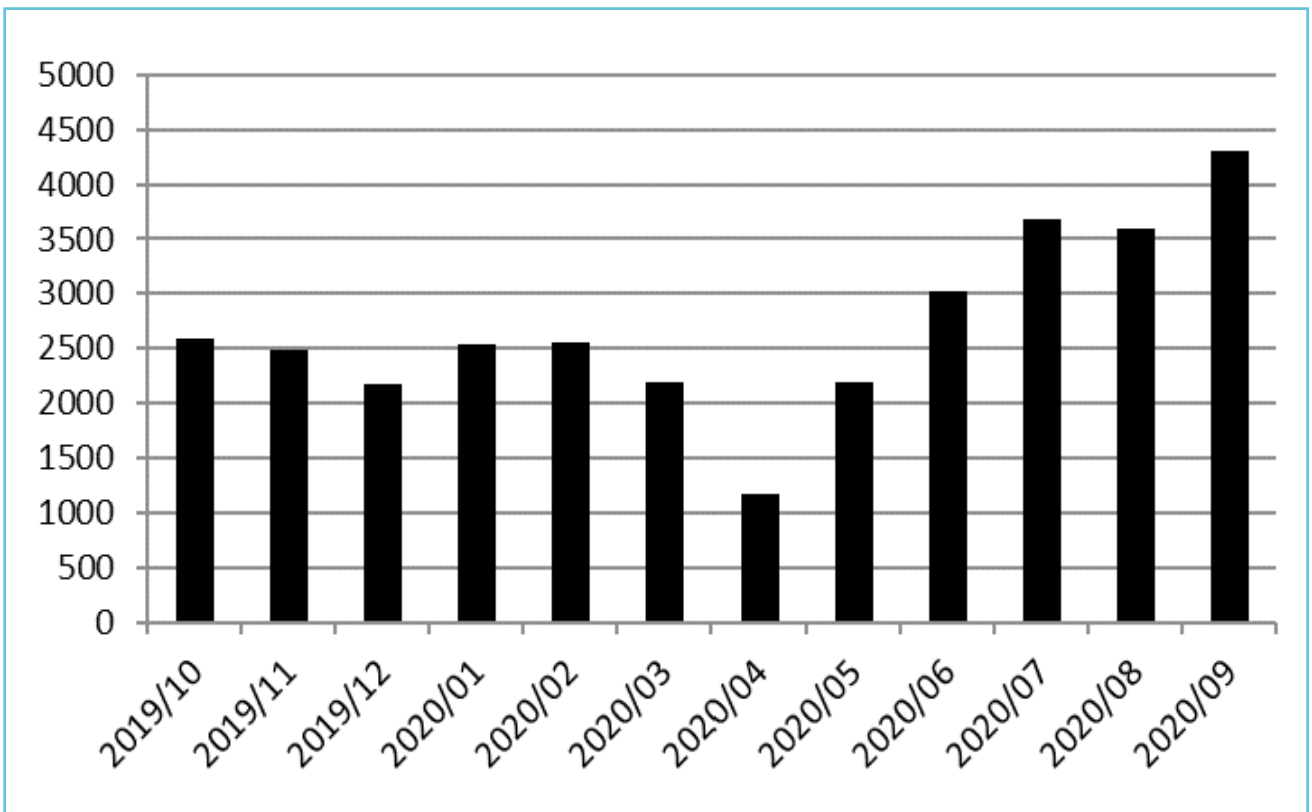
appropriate for high FIT results. FIT results are available to the gastroenterologists vetting requests thus providing added information to the clinical details. This approach has been rolled out to all 14 Scottish Health Boards over the last five years utilising the same analytical platform and clinical action limits and, in our opinion, is the one of the very few routine laboratory test to achieve uniform use in NHS Scotland.



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Figure 2 Number of FIT requests analysed by Blood Sciences, NHS Tayside from October 2019 to September 2020



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