Supplement 2

Implementation & Research Recommendations

Implementation of Faecal Immunochemical Testing (FIT)

Implementation of FIT in symptomatic colorectal cancer pathways should be a "locally agreed" collaboration between primary and secondary care, which should include a process of education in the use of FIT testing to ensure confident and safe use. Early discussions between stakeholders in primary care, secondary care, pathology laboratories and IT services are key to effective pathway development. Local healthcare systems, need to ensure adequate resources are in place for appropriate staffing in primary and secondary care to provide timely response to elevated FIT results and downstream pathways. This will need to include effective IT support, equipment, staff and appropriate accreditation in pathology laboratories that undertake FIT[1]It is also important to ensure that there is an effective process for FIT kit distribution, education about sampling, processes to avoid delayed action following "positive" FIT tests and identify non-return of FITs.

Pathways:

The majority of patients with bowel symptoms and signs raising suspicion of Colorectal Cancer will be triaged using FIT. This will include patients with Rectal Bleeding and Iron Deficiency Anaemia. Clinical Assessment of the patient remains an important part of patient evaluation when using FIT. All patients should undergo abdominal and PR examination and those found to have a palpable anorectal mass or anal ulceration should be directly referred on a "fast-track" pathway without a FIT test. (Figure 1)
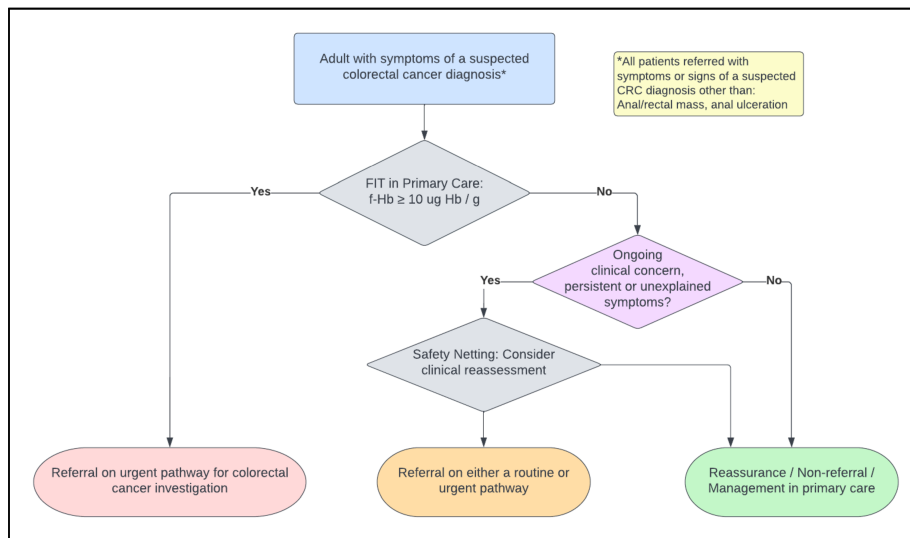
Figure 1: Pathway for Use of FIT in Patients with Signs or Symptoms Raising Suspicion of Colorectal Cancer (CRC) (including those with rectal bleeding, and iron deficiency anaemia).

Complementary pathways are also fundamental to effective roll out and management in Primary Care. Direct access routine gastroscopy for asymptomatic anaemia, as recommended by NICE[2], direct access routine flexible sigmoidoscopy and "vague symptom" pathways are all well described. New pathways that allow patients with FIT results below the threshold for urgent suspected cancer referral to be rapidly vetted and assessed by a lower GI specialist (without triggering timed pathways) should also be considered. In some cases, the outcome may be no investigation even after referral and specialist review, as is supported by data from utilisation of FIT within urgent suspected cancer pathways in Scotland[3].

Safety netting:

Providers should establish appropriate safety-netting mechanisms for patients returning fHb results below the threshold adopted for "urgent suspected CRC" referral but for whom there remains clinical concern in primary care, for those who do not engage with the test, and for those who are not referred following a positive FIT result. Examples of safety netting and advice given in established FIT pathways are provided in Appendix I. More generic advice on safety netting is also widely available[4–6].

GP and specialist education:

Collaborative local education programmes enable effective implementation of locally agreed services. It is key that those requesting the test are provided with clear information about the local process for "Fast Track" referral of patients with "positive" (above the threshold) FIT results and those for patients with sub-threshold FIT (or absent FIT result) . This information should also cover related pathways, including alternate cancer, vague symptom and urgent concern pathways and these should be developed alongside FIT implementation where possible.   Optimally education programmes should commence before "go live" of these new pathways.

Kit distribution:

Established pathways have adopted a variety of methods for kit distribution and return. There are some pathways where FIT is requested electronically and posted to the patient[7]. These electronic process can create an immediate audit trail and may be triggered by a virtual consultation. They can also link to results reporting and provide additional text to guide the clinician on appropriate next steps[8] . Future developments may include "Point of care testing platforms"[9].

Sampling errors:

Use of FIT is usually dependent on the patient for sampling and so clear patient information is important to guide appropriate sample collection Easy to follow instructions are available to guide patients on how to collect samples. The graphical nature of these instructions can help to avoid language barriers. Charities, BCSP and FIT companies have templates that can be adapted for use in local symptomatic pathways[10]. The needs of frailer patients or others who may struggle to sample effectively must also be addressed. Some groups have described taking the FIT sample at the time of digital rectal examination (DRE)[10]

Some pathways include explicit instructions to avoid sampling when overt blood is visible to reduce "false positives", and some also advise women to avoid sampling if blood is visible

during menstruation. These pathway modifications are noted for interest but are not included in our recommendations as the evidence is lacking.

Non-return of FITs

Patients should be advised to return their kits soon after sampling to avoid degradation of faecal haemoglobin – prolonged storage or transit, particularly at high temperatures, may increase the risk of sub-threshold fHb results in samples that would otherwise yield results over the threshold for urgent CRC referral[1]. In pathways where the FIT kit is handed to the patient in primary care the date should be recorded and processes should be developed to flag kits that have not been returned within a locally agreed timeframe. Patients should also be asked to make note on the FIT request of the date the sample was collected.

FIT results reporting

The numerical value of the fHb result (the fHb concentration) must be reported to the requester, in preference to solely a positive or negative result. Advice or a link to the locally recommended GP action based on the FIT result can be included with the FIT result to assist decision making in primary care, including alternative pathways for FIT negative cases of low clinical concern for serious colorectal disease, discussion with the laboratory will enable a tailored response to be developed.

Facilitators & Barriers:

We expect that NHS organisations including commissioners and policy makers will engage with clinicians to implement the guideline for the benefit of people with signs or symptoms of suspected CRC. The cooperation of professional bodies from primary and secondary care should promote implementation, develop training materials for clinicians, and liaise with local champions to arrange learning events.

Audit and surveillance:

All pathways using FIT should incorporate mechanisms to audit clinical outcomes. These should include colorectal and other serious disease outcomes, flagging and tracking of patients not referred but with positive FITs, flagging and feedback of patients referred without a FIT, and diagnostic intervals in patients with colorectal cancer with and without FIT

in their pathway. Variations in uptake and use of FIT in primary care should also be monitored. The impact of introduction of FIT in colorectal cancer pathways, such as UGI cancer pathways, vague symptoms and routine pathways, should also be measured, as well as the downstream impact on diagnostics. An audit tool should be developed and suggested data points for monitoring are presented in Appendix II.

References

1. Godber, I. M., Benton, S. C. & Fraser, C. G. Setting up a service for a faecal immunochemical test for haemoglobin (fit): A review of considerations, challenges and constraints. *Journal of Clinical Pathology* **71**, 1041–1045 (2018).

2. Suspected cancer: recognition and referral. NICE guidelines [NG12]. vol. 2021 https://www.nice.org.uk/guidance/ng12/chapter/Introduction (2015).

3. Johnstone, M. S. *et al.* Combining the quantitative faecal immunochemical test and full blood count reliably rules out colorectal cancer in a symptomatic patient referral pathway. *International Journal of Colorectal Disease* (2021) doi:10.1007/s00384-021-04079-2.

4. Nicholson, B. D., Mant, D. & Bankhead, C. Can safety-netting improve cancer detection in patients with vague symptoms? *BMJ* **355**, i5515 (2016).

5. NICE. Safety netting. https://www.nice.org.uk/guidance/ng12/chapter/recommendations-on-patient-support-safety-netting-and-the-diagnostic-process#safety-netting.

6. Safety netting. *Safety net* https://www.cancerresearchuk.org/health-professional/diagnosis/suspected-cancer-referral-best-practice/safety-netting.

7. Chapman, C. *et al.* Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. *BJS Open* **3**, 395–402 (2019).

8. Chapman, C. *et al.* Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham. *Colorectal Disease* **22**, 679–688 (2020).

9. Khan, A. A., Klimovskij, M. & Harshen, R. Accuracy of faecal immunochemical testing in patients with symptomatic colorectal cancer. *BJS Open* **4**, 1180–1188 (2020).

10. FIT   instructions. https://www.cancerresearchuk.org/sites/default/files/fit_symptomatic_patient_leaflet_final.pdf.

11. Mellen, S. *et al.* Evaluation of sample stability for a quantitative faecal immunochemical test and comparison of two sample collection approaches. *Annals of Clinical Biochemistry* **55**, 657–664 (2018).

Appendix I : Pathways & Safety Netting:

a) **Symptomatic FIT Safety Netting Guidance:**
   - Tayside   https://www.gov.scot/publications/coronavirus-covid-19-guidance-for-use-of-fit-testing-for-patients-with-colorectal-symptoms/

   - Oxford https://thamesvalleycanceralliance.nhs.uk/our-work/cancer-prevention-and-early-diagnosis/fit-symptomatic/

   - Nottingham http://www.fit-screening.co.uk/about-us/news/Nottingham_Fit

   - Croydon   https://www.swlpath.nhs.uk/wp-content/uploads/2019/12/Croydon-FIT-testing-GP-information-leaflet.pdf

   - *https://www.swlpath.nhs.uk/test-information/faecal-immunochemical-test-fit/fit-testing-in-croydon/*

b) **Generic Safety Netting:**
   - Safety netting | Cancer Research UK

   - Recommendations on patient support, safety netting and the diagnostic process | Suspected cancer: recognition and referral | Guidance | NICE

   - https://www.cancerresearchuk.org/sites/default/files/fit_symptomatic_patient_leaflet_final.pdf

Appendix II Proposed dataset for FIT audit and CRC diagnoses

Patient characteristics: demographics (age, sex, postcode), symptoms leading to FIT, referral criteria when not prompted by FIT, blood test results (e.g. haemoglobin, mean cell volume, platelets, ferritin), medications (e.g. aspirin, warfarin), family history of colorectal cancer.

FIT requests: numbers requested (primary care / secondary care), threshold adopted, continuous FIT value, proportion returned, sample time, processing time, analyser.

Pathology: colorectal cancer (site, stage), other cancers, low risk adenoma, high risk adenoma requiring follow up as per BSG, SPECC, diverticular disease (complicated, uncomplicated), haemorrhoids, colitis (macroscopic, microscopic), benign upper GI pathology if OGD done, normal, other.

Monthly demand: GP referrals (routine, colorectal 2WW), colonoscopy, flexi sigmoidoscopy, CT colonography, screening participation.

Every new cancer diagnosis screened for:

Colonoscopy in previous 3 years

CTC in previous 3 years

FIT in previous 3 years

Clinical and pathway outcomes

Time to first test from FIT request and from 2WW referral

Time to tissue diagnosis from FIT request and 2WW referral

Type of first test

Time to patient receiving diagnosis from FIT request and 2ww referral

Time to First definitive treatment (FDT) from FIT request and 2WW referral

TNM stage of CRCs detected on 2WW pathways and Routine pathways

FDT of CRCs detected on 2WW pathways and Routine pathways

Research Questions

1.1 Background

There will not be a perfect test which will detect and diagnose all cases of CRC in symptomatic populations, and the role of specific test such as FIT, needs to be placed into the wider context of a test which is not diagnostic, but identifies those likely to benefit from colorectal investigation.

Development of this guideline on the use of FIT in patients with signs or symptoms of suspected colorectal cancer has been undertaken with rigorous evaluation of the published literature. However throughout this guideline we recognise that data is limited, much of the information and recommendations are based on observational data, and that further refinement and development of the evidence base is required, especially where we have stated "there is currently insufficient evidence" to provide recommendations. In addition the GRADE of evidence is predominantly low, based on largely observational data. Thus we have prioritised research questions to address these knowledge gaps, specifically where further research will be important to further develop the use of FIT.

1.2 Method

Research questions were identified by members of the Guideline Development Group (GDG), as well as in Delphi rounds 1 and 2 from the extended-Delphi group. In round 3 of Delphi GDG members were asked to rank the research questions by their importance, and all the questions were then discussed and agreed, with the top 5 questions determined, and further important questions were listed but not ranked. Where a statement indicated that 'there was insufficient evidence', or where there is clear need to develop evidence to answer key questions about the use of FIT in a symptomatic population a research question was specifically developed.

1.3 Top 5 research questions

1. What is the impact of FIT in a symptomatic population in terms of CRC survival and other critical outcomes?

2. Is the stage of diagnosis of CRC altered by the use of FIT testing in symptomatic patients?

3. Can faecal haemoglobin be combined with other factors/biomarker(s) to improve the accuracy of CRC detection? (e.g. genomic risk scores or other biomarkers)

4. Does a repeat / second FIT enhance diagnostic accuracy?

5. What safety-netting strategies may be employed to avoid missed CRC diagnosis in patients with a FIT below different concentrations of f-Hb?

1.4 Other key research questions

- What are the benefits and harms of using FIT to guide investigation of patients with lower GI symptoms, for example in terms of time to diagnosis, and risk of emergency presentation at diagnosis?

- What is the performance of colorectal investigations (e.g. colonoscopy, CT, CCE) according to different f-Hb concentrations?

- What is the Diagnostic Accuracy of FIT for CRC in people with bowel symptoms?

- What patient related factors are relevant (e.g. age, gender) at different concentrations of f-Hb?

- What is the health economic impact of the use of FIT in symptomatic populations (including sub-groups e.g. age, gender, various symptoms)?

- What are the barriers to the use of FIT in symptomatic populations?

- What is the post-FIT colorectal cancer rate at different concentrations of f-Hb (corollary of PCCRC)?

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- Does the type of FIT analyser used affect the Sensitivity and Specificity of FIT for detection of CRC in patients with symptoms suggestive of CRC?

- What is the experience of patients in the diagnostic pathway to CRC diagnosis who undergo FIT testing?

- How does FIT result vary with time of day and bowel frequency?

- What proportion of patients (with different concentrations of f-Hb) undergo colonoscopy or other colorectal imaging?

- What is the frequency of cancer in symptomatic patients with different concentrations of f-Hb who undergo normal colonoscopy?

1.5: Top 5 research questions: Suggested areas for further evaluation

Q1 What is the impact of FIT in a symptomatic population in terms of CRC survival and other critical outcomes?

Q2. Is the stage of diagnosis of CRC altered by the use of FIT testing in symptomatic patients?

Larger evaluations of stage of CRC diagnoses and survival rates are needed, comparing positive FIT CRC diagnoses, with no FIT CRC diagnoses and negative FIT CRC diagnoses. Determining the health economic impact resulting from these potential improvements will facilitate optimal implementation. Studies are required describing and comparing time to diagnosis, stage at diagnosis, survival, and mortality between patients with and patients without FIT as part of their diagnostic pathway. A stage-shift would be key to improving outcomes but can only achieved by a clinically effective threshold and a collaborative approach between Primary and Secondary Care.

Q3 Can faecal haemoglobin be combined with other factors/biomarker(s) to improve the accuracy of CRC detection? (e.g. genomic risk scores or other biomarkers)?

There is some supporting and emerging evidence that combining faecal haemoglobin with either a composite score or another biomarker, improves CRC detection. However these methods have not yet been clinically validated. Therefore further studies are required to determine the better combination of test (e.g. AI tools, polygenic risk score, novel biomarkers) or risk assessment alongside FIT, and if it is patient acceptable and cost effective. A clinical trial (NIHR127800) is underway to answer the research question around the benefits of combined use of marker(s) with faecal haemoglobin to detect bowel disease.

Q4 Does a repeat / second FIT enhance diagnostic accuracy?

Currently there is insufficient evidence to support the use of a repeat or second FIT test. Further studies would provide information on potential benefits of increased sensitivity and specificity which may be helpful in informing the evaluation of patients with ongoing symptoms following a FIT result below threshold as part of the safety netting process. If more than one FIT is found to be helpful then it will also be important to evaluate the timing of this additional test.

Q5 What safety-netting strategies may be employed to avoid missed CRC diagnosis in patients with a FIT below different concentrations of f-Hb?

Clarification of the outcomes of investigation of the natural history of CRC and symptom duration to inform safety-netting intervals is required. Studies may be designed to derive the most effective investigative strategy to identify colonic and non-colonic gastrointestinal malignancy in FIT 'below the threshold' patients. Communication and standardisation of reporting (e.g. format of FIT report) to encourage GP action following an abnormal result is needed. E-safety-netting solutions should be developed to ensure that safety-netting is conducted and standardized for all patients.

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1.6 Summary:

Development of this Guideline has identified a number of areas where published data is lacking. Key areas for further investigation have been generated and prioritised by the Guideline Development Group and e-Delphi process. Standardisation of metrics across different study cohorts in generating higher quality data may inform future iterations of this guideline. Some of these questions are currently undergoing evaluation through existing national clinical programmes and technological assessments, and may contribute to future update of this guidance as new data is generated.