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Faecal immunochemical testing (FIT) in patients with signs or symptoms of suspected colorectal cancer (CRC): a joint guideline from the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG)

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ABSTRACT

Faecal immunochemical testing (FIT) has a high sensitivity for the detection of colorectal cancer (CRC). In a symptomatic population FIT may identify those patients who require colorectal investigation with the highest priority. FIT offers considerable advantages over the use of symptoms alone, as an objective measure of risk with a vastly superior positive predictive value for CRC, while conversely identifying a truly low risk cohort of patients. The aim of this guideline was to provide a clear strategy for the use of FIT in the diagnostic pathway of people with signs or symptoms of a suspected diagnosis of CRC. The guideline was jointly developed by the Association of Coloproctology of Great Britain and Ireland/British Society of Gastroenterology, specifically by a 21-member multidisciplinary guideline development group (GDG). A systematic review of 13 535 publications was undertaken to develop 23 evidence and expert opinion-based recommendations for the triage of people with symptoms of a suspected CRC diagnosis in primary care. In order to achieve consensus among a broad group of key stakeholders, we completed an extended Delphi of the GDG, and also 61 other individuals across the UK and Ireland, including by members of the public, charities and primary and secondary care. Seventeen research recommendations were also prioritised to inform clinical management.

OBJECTIVE

To provide a clear strategy for the use of faecal immunochemical testing (FIT) in the diagnostic pathway of people with signs or symptoms of a suspected diagnosis of colorectal cancer (CRC).

BACKGROUND

Evaluation in primary care of symptomatic patients with a potential diagnosis of CRC is challenging. Symptoms alone are unreliable predictors of those who may have a diagnosis of CRC and may therefore result in a high proportion of eligible patients not having access to diagnostic examination. Use of FIT offers considerable advantages over the use of symptoms, with a vastly superior positive predictive value (PPV) for CRC, while conversely identifying a truly low risk cohort of patients. FIT provides an opportunity to effectively triage patients with bowel symptoms into two groups: those who require 'Fast Track' referral on an urgent suspected cancer pathway and lower risk patients who may potentially be managed in primary care. The benefit of this stratification should be to reduce the fear of missed/delayed diagnosis of CRC which is currently driving high referral rates for investigation, enabling more effective use of investigative processes with a focus on evaluating those with a significant risk of an underlying CRC diagnosis.

Through the COVID-19 pandemic, FIT has been increasingly employed across the UK, in an ad hoc way in primary and secondary care, leading to significant variation in practice. The purpose of this guideline is to provide an evidence-based framework for the optimal use of FIT in the diagnostic pathway for people with symptoms or signs of a suspected diagnosis of CRC.

METHODS

This guideline was jointly commissioned by the Association of Coloproctology of Great Britain and Ireland (ACPGBI), and British Society of Gastroenterology (BSG), and a guideline chair selected from each society (MMD and KJM). It was developed in accordance with the BSG National Institute of Health and Care Excellence (NICE)-accredited guideline process.

The guideline development group (GDG) included colorectal surgeons (MMD, MA, AB, MM and RJCS), nurse specialist (MP) and gastroenterologists(RA, JEE and KJM) nominated by ACPGBI and BSG (co-leads MMD and KJM), general practitioners (GPs: BDN and LSa), a professional

guideline methodologist (JK), an epidemiologist (LSh), a clinical biochemist (SB), radiologists from the British Society of Gastrointestinal and Abdominal Radiology (DB and JS), patient representatives (JP and NB) and three colorectal surgical research fellows (ND, RB and RVC), and was selected to ensure wide-ranging but relevant expertise across all relevant disciplines. An invited 92 member four-nation multidisciplinary group participated in the extended-Delphi (online supplemental file 1). All members of the GDG, and participants in the extended Delphi process completed a Declaration of Conflict of Interests (COI) form which was reviewed and vetted by the chairs.

SCOPE

A scoping meeting was held on 20th May 2021, and in advance of this meeting the GDG was asked to develop key priorities and questions. It was agreed that the scope of this guideline was to develop guidelines for the role of FIT testing in patients with signs and symptoms of a suspected diagnosis of CRC. The target audience are clinicians involved in this pathway from primary care through to secondary care.

FIT has a high sensitivity and PPV compared with the use of symptoms alone to determine the need for referral from primary care to secondary care for further diagnostic investigation for people with symptoms or signs of a suspected diagnosis of CRC. The sensitivity of FIT for what is known as other 'serious bowel disease' (including advanced adenomas, inflammatory bowel disease) is considerably lower than for CRC, and as such this guideline focuses on the role of FIT in the diagnostic pathways for CRC. Similarly, this guideline is not designed to provide advice for the investigation management of gastrointestinal (GI) symptoms outside the context of FIT in the diagnostic pathway for suspected CRC.

The GDG agreed that these guidelines should stimulate greater efforts to ensure access to FIT for all GPs and eligible patients, and should therefore include advice designed to facilitate implementation.

The GDG developed key questions for the guideline:

1. What FIT thresholds should be used to trigger referral from primary care?
2. Should FIT be used in primary care or secondary care?
3. What advice can we offer clinicians where patients have not returned an FIT test?
4. What safety netting strategies may be employed to avoid missed CRC diagnosis in patients with an FIT below the chosen threshold?
5. What is the diagnostic accuracy of FIT for CRC with specific symptoms?
6. Does diagnostic accuracy vary by patient-related factors (eg, age-group, sex, ethnicity and deprivation)?
7. Is a repeat/ second FIT useful and does it enhance diagnostic accuracy?
8. Does the diagnostic accuracy of FIT vary with the type of analyser used?
9. Should FIT be combined with other factors to optimise risk stratification?
10. Can FIT be used in specific populations, for example, young symptomatic patients to facilitate early diagnosis of early onset CRC?
11. Is there a role for specific interventions according to patient or test related factors? Can FIT (faecal haemoglobin (fHb) levels) be used to prioritise investigations?
12. What is the acceptability of FIT in patients with suspected CRC symptoms and their treating clinicians?
13. How can we avoid discriminating against certain populations in this guideline?
14. What lessons may be learnt from implementation programmes of FIT in symptomatic populations?

The GDG agreed that FIT should not be a sole arbiter of referral. Therefore patients who do not have signs or symptoms of a suspected diagnosis of CRC have not been considered within this guideline, and furthermore should not be referred from primary care outside the context of national screening programmes because of an FIT test alone. Conversely those with an FIT below threshold may be managed in primary care, but should not be denied access from referral to secondary care if referral is appropriate for other reasons. Such patients may be referred on routine or urgent pathways, but not necessarily on the suspected CRC investigation pathway. Patients with signs of an abdominal mass should be referred urgently, however an FIT should be requested simultaneously in primary care in order to inform subsequent investigation. Those with an anal/rectal mass or anal ulceration should be referred urgently from primary care without an FIT.

PICOS, SEARCH STRATEGY AND GRADE

Three broad PICOs (patients, interventions, controls and outcomes) were developed which considered these questions (online supplemental file 1). The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument provided a methodological framework.[1]

Search strategies agreed by the GDG, and a systematic literature search was performed by four members of the GDG (MA, ND, RVC and RB), which returned 100 publications. Additional references were obtained by cross-referencing and by recommendation from the GDG. Relevant published national and international guidelines were also scrutinised. After each round of Delphi, and before the guideline was finalised, the search was repeated, and any important studies published since the initial evidence search incorporated.

A modified electronic Delphi process[2] was used to develop and refine statements. Initial draft statements formulated by the writing committee were reviewed by the GDG to allow for modification and to identify additional references. After a preliminary discussion, formal anonymous voting rounds were undertaken using SurveyMonkey. Each statement was scored by each member of the GDG using a 5-point Likert scale. We invited also key national and international opinion leaders from the ACPGBI, BSG, primary care, clinical biochemistry, patient representation (who contributed to the online supplemental Lay Summary) and CRC charities to participate in the modified Delphi process. We included additional patient and public involvement in the Delphi process by inviting participants through the national charities Bowel Cancer UK and Bowel Research UK. Consensus required at least 80% agreement. Where consensus was not reached, feedback from the GDG members was disseminated after each round to allow members to reconsider their original position.[3] Where appropriate, revisions to statements were made and a further voting round was undertaken in second and third rounds, with a summary flowchart agreed by the GDG (figure 1).

The GDG also developed research recommendations (online supplemental file 2) which were prioritised by electronic voting.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool[4] was used to evaluate the strength of evidence and the strength of recommendations made (see Executive summary of recommendations). The GRADE system specifically separates the strength of evidence from the strength

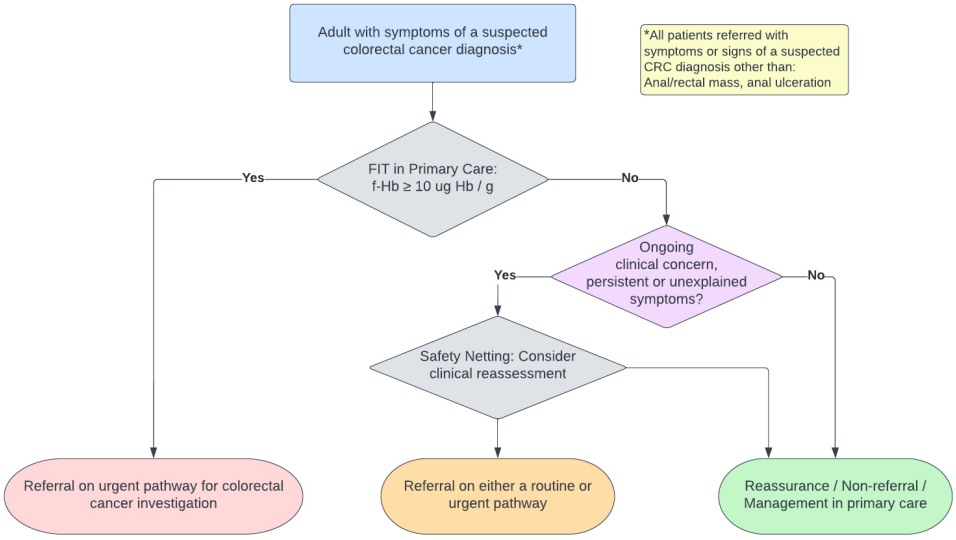

Figure 1 Pathway for FIT in patients with signs or symptoms of a suspected diagnosis of colorectal cancer (CRC), including symptoms such as those with per rectal bleeding, and signs including iron deficiency anaemia. Those with an abdominal mass should be referred urgently, but an FIT should be sent simultaneously in primary care in order to inform subsequent management. FIT, faecal immunochemical testing, fHb, faecal haemoglobin.

of a recommendation. While the strength of a recommendation may often reflect the evidence base, the GRADE system allows for occasions where this is not the case—for example, where it seems good sense to make a recommendation despite the absence of high-quality scientific evidence such as a large randomised controlled trial (RCT). ACPGBI and BSG commissioned Kleijnen Systematic Reviews (an independent research company), to undertake the GRADE process, using the outcomes of the literature search and specialist input from the GDG.

The health benefits, side effects and risks of the use of FIT in symptomatic patients have been considered in formulating the recommendations. It was agreed that when recommendations were developed the GDG considered the impact of FIT testing in terms of CRC diagnosis should be balanced with the risks of harm (for example, compared with colonoscopy complications or psychological distress) and the relative costs to both the health service and patients. We have developed pragmatic implementation guidance, and research questions designed to inform future iterations of these guidelines (online supplemental file 2). Further work will be required to facilitate implementation such as the development of training for primary care, management of diagnostic resources and refinement of a draft audit tool included in the implementation section in order to measure the impact of the guideline. The costs and consequences associated with the implementation of these guidelines will require health economic evaluation (in the absence of currently available cost-effectiveness evidence), and a research question has been developed related to this requirement (online supplemental file 2).

TOP OF FORM

Executive summary of recommendations

FIT in primary care

1. We recommend that FIT should be used by primary care clinicians to prioritise patients with clinical features of CRC for referral for urgent investigation
2. We recommend that an FIT threshold of fHb ≥10 µg Hb/g should be used in primary care to select patients with lower GI symptoms for an urgent referral pathway for CRC investigation.
3. We recommend that patients should not be excluded from referral from primary care for symptoms on the basis of FIT testing alone

Advice for clinicians where patients have not returned an FIT test

4. We suggest that clinicians should follow-up patients with no FIT result to encourage them to return a sample or, where the kit has been lost or inadequately submitted, offer a further test.
5. We suggest that patients who decline to return an FIT test should be counselled that evaluation of their symptoms is incomplete, and be encouraged to complete their test
6. We suggest that where no FIT result can be obtained, clinicians should use existing national and local guidelines to assess risk of CRC.

Safety netting

8. We recommend that some patients with symptoms of suspected CRC may be managed in primary care if fHb <10 µg Hb/g, and provided appropriate safety-netting is in place.
9. We suggest that patients with an fHb <10 µg Hb/g but with persistent and unexplained symptoms for whom the GP has ongoing clinical concern should be referred to secondary care for evaluation
10. We recommend that safety-netting protocols should incorporate advice and strategies for the diagnosis of CRC and extracolonic cancer, as well as other serious gastro-intestinal conditions.

Diagnostic accuracy of FIT for CRC with suspected cancer signs or symptoms

11. FIT is a triage tool to identify those patients with symptoms of suspected CRC who should undergo further colorectal investigation
12. We suggest that FIT be used for people with iron deficiency anaemia within primary care to inform urgency of referral
13. We suggest referral of patients with persistent/recurrent anorectal bleeding for flexible sigmoidoscopy if fHb <10 µg Hb/g

14. There is currently insufficient evidence to recommend variations in the fHb threshold for referral from primary care according to patient related-factors
15. There is currently insufficient evidence to confirm whether diagnostic accuracy is impacted by the type of FIT analyser used.
16. There is currently insufficient evidence to recommend including FIT in a risk score with other clinical features to identify patients with symptoms of suspected CRC.
17. We suggest that FIT may be used to stratify adult patients aged younger than 50 years with bowel symptoms suspicious of a diagnosis of CRC.

Investigation in secondary care

18. Colonoscopy is considered the standard method of investigation, however other methods of colorectal imaging may be appropriate in some patients
19. We recommend that for patients with symptoms of a suspected diagnosis of CRC, CT colonography (CTC) is equivalent to colonoscopy for detection of CRC (the choice of modality should be determined by the local expertise and availability).
20. There is currently insufficient evidence to support use of a specific quantitative FIT threshold to recommend the selection of CT colonography versus colonoscopy

Acceptability

21. On the basis of limited evidence, clinicians and patients consider FIT as an acceptable test for symptomatic CRC in most circumstances
22. We recommend that services should consider ways of promoting a high proportion of patients to return FIT kits.

Discrimination

23. We recommend that clinicians actively prevent discrimination at any stage of the diagnostic pathway as symptomatic FIT testing is rolled out, with a focus on equity of access and application to all patients with lower GI symptoms

Implementation

24. We recommend that FIT, as a diagnostic triage tool, can be implemented safely at primary care level, and that a programme of education be developed to facilitate implementation of FIT in primary care.

FIT IN PRIMARY CARE

We recommend that FIT should be used by primary care clinicians to prioritise patients with clinical features of CRC for referral for urgent investigation

GRADE of evidence: low; Strength of recommendation: Strong.

We recommend that an FIT threshold of fHb ≥10μg Hb/g should be used in primary care to select patients with lower GI symptoms for an urgent referral pathway for CRC investigation.

GRADE of evidence: low; Strength of recommendation: Strong.

We recommend that patients should not be excluded from referral from primary care for symptoms on the basis of FIT testing alone.

GRADE of evidence: very low; Strength of recommendation: Strong.

An FIT≥10 µg Hb/g faeces is recommended by NICE to select patients for an urgent '2-week-wait' (2WW) referral for CRC investigation.[5] This recommendation has not changed since it was introduced in 2017 despite the guidance changing on which patient groups, symptoms, signs or anaemias should trigger an FIT in primary care.[5 6] When NICE set the threshold at ≥10 µg Hb/g faeces there was a paucity of data available on FIT in symptomatic patients tested in primary care prior to referral for colonic investigation.[7] Since 2017, numerous studies have been published to inform the choice of FIT threshold in primary care,[8–20 20–23] including some showing that FIT outperforms symptom-based referral criteria.[24–26]

Although the choice of FIT thresholds has an important role in the allocation of resources, the primary rationale for the selection of an fHb threshold is to ensure that a symptomatic population is offered interventions relative to absolute CRC risk. Symptomatic populations with an fHb below a defined threshold may theoretically not be indicative of increased CRC risk compared with an asymptomatic population, and therefore we sought to determine this risk according to fHb concentration.

Randomised controlled trials

There have been no RCTs comparing time to diagnosis, stage at diagnosis or longer-term CRC outcomes between patients with and patients without FIT as part of their diagnostic pathway, nor any trials comparing FIT based pathways using different FIT thresholds.

Systematic review of cohort studies of primary care patients

A systematic review summarised the diagnostic performance of FITs for CRC across a range of thresholds, including 69 536 symptomatic adults from primary care from 23 cohort studies published between May 2018 and November 2020.[26] Using the reported limit of detection (LoD), which ranged from ≥2 µg Hb/g faeces to ≥7 µg Hb/g faeces, meta-analysis of 11 studies (n=41 388 patients) resulted in a pooled sensitivity of 93.4% (95% CI 88.0% to 96.4%) and specificity of 76.9% (95% CI 67.7% to 84.0%). At a threshold of ≥10 µg Hb/g faeces (15 studies; n=48 872), pooled sensitivity was lower at 87.0% (95% CI 81.0% to 91.6%) with higher specificity 84.4% (95% CI 79.4% to 88.3%). Meta-analysis of five studies (n=24 187) reporting at ≥20 µg Hb/g faeces resulted in a reduced sensitivity of 84.1% (95% CI 78.6% to 88.4%) and an increased specificity of 86.6% (95% CI 75.6% to 93.1%). At a threshold of ≥150 µg Hb/g faeces meta-analysis of six studies (n=34 691) resulted in a sensitivity of 64.1% (95% CI 57.8% to 69.9%) and a specificity of 95.0% (95% CI91.2% to 97.2%).

Primary care cohorts with low prevalence of CRC

The underlying prevalence of CRC directly influences a test's performance at a chosen threshold. Individual prospective and retrospective cohort studies reporting FIT performance in populations of patients tested in primary care report CRC prevalence ranging from 0.8% to 1.8%, highlighting the variation in symptomatic patient groups eligible for FIT across primary care settings.[8 11 13 18 20 21] In a subgroup analysis of the review, at a threshold of ≥10 µg Hb/g faeces, sensitivity was lower at 86% (95% CI 78% to 93%) versus 89% (95% CI 82% to 96%) and specificity significantly higher of 87% (95% CI 82% to 92%) versus 81% (95% CI 74% to 88%) when eight studies with a combined prevalence <3% were compared with seven studies with a prevalence of ≥3%.[26]

Trade-offs between single FIT thresholds in primary care cohorts

Most cohort studies have reported the use of a single FIT threshold with some including statistical modelling to demonstrate the

trade-offs at different FIT thresholds in terms of the numbers needed to scope (NNS) to detect one cancer and the number of missed cancers (NMC) per 1000 patients tested.

The review reported that for a prevalence of 1% and 2%, the NNS was 20 and 10 using a threshold of ≥10 µg Hb/g faeces, and the NMC was 1 and 3 per 1000 patients, respectively.[26] Increasing the threshold to ≥20 µg Hb/g faeces reduced the NNS to 12 and 6 and the NMC increased to 2 and 4 per 1000 patients tested. At 150 µg Hb/g faeces the NNS is reduced further to 7 and 4, and the NMC increased to 4 and 8 per 1000 patients tested.

Based on a large retrospective cohort of 9896 patients tested in English primary care in the context of the DG30 NICE guidelines (CRC prevalence 1.1%), the authors illustrated the NNS and NMC for the thresholds of ≥7, 10, 20, 50, 100, 120 and 150 µg Hb/g faeces.[27] The corresponding proportion of positive tests were 11, 10, 7, 4, 3, 3 and 2%, the proportion of cancers detected 91, 91, 85, 74, 61, 57 and 54%, the NNS to detect one cancer was 11, 10, 8, 6, 5, 5 and 4, and the NMC per 1000 FITs was 1, 1, 2, 3, 4, 5 and 5. Reducing the threshold of ≥10 to ≥2 µg Hb/g faeces resulted in increase in the NNS to 21 and a reduction in the NMC to 4 per 100 000 patients tested.[23]

At a higher prevalence of 1.6%, a smaller Spanish retrospective cohort of 4543 symptomatic patients reported the NMC per 1000 patients tested to be 3.7 (2.2–6.3) at a threshold of ≥10 µg Hb/g faeces compared with 4.1 (2.5–6.6) using ≥20 µg Hb/g faeces, and the NNS was 13.8 (10.8–17.7) compared with 10.9 (8.5–14.0).[27] The authors concluded that the use of ≥20 µg Hb/g in preference to ≥10 µg Hb/g could reduce referrals for colonoscopy without missing more than one CRC per 1000 patients tested.

Increasing the threshold favours specificity reducing the NNS to detect one CRC but increases the NMC per 1000 patients tested. The opposite occurs when the threshold is reduced. The FIT threshold used in clinical practice is likely to be chosen based on a balance of tolerance of missed cancers and the diagnostic resources available to urgently investigate CRC.

Multiple thresholds for low-risk, intermediate-risk and high-risk populations

Multiple FIT thresholds have been introduced in some clinical settings to provide a rule-out threshold, a rule-in threshold and an intermediate range where the investigation of population subgroups and/or active safety netting is advised.

The Nottingham rapid CRC diagnosis (RCCD) service triages adult patients of any age, except those with rectal bleeding and rectal mass, combining low, intermediate and high thresholds (prevalence 1.6% (227/13 361)).[10] The RCCD service considers ≥100 µg Hb/g faeces the 'high risk' positive contacting these patients directly for rapid investigation. Patients with an FIT result <4 µg Hb/g faeces, and with an FIT result of 4–10 µg Hb/g faeces but normal blood tests are considered 'negative'. Patients with an FIT of 4–10 µg Hb/g faeces with anaemia, low ferritin or thrombocytosis, or with FIT ≥10 µg Hb/g faeces are considered 'positive' and investigated urgently via the 2WW. The cancer detection rate was 0.1% for <4 µg Hb/g faeces, 0.6% between 4 and 9.9 µg Hb/g faeces, 3.3% for 10–99.9 µg Hb/g faeces and 20.7% for ≥100 Hb/g faeces.

Cohort data from Tayside on FIT use in primary care patients with unselected GI symptoms was modelled to show that 'reassurance thresholds' of <2, 7, 10 and 20 µg Hb/g faeces were associated with CRC risks of 0.1, 0.3, 0.3 and 0.4%.[18] Intermediate-risk populations were created to highlight those with a cancer risk below the 3% risk used by NICE to trigger urgent colorectal investigation. For example, an intermediate population defined by 10–99 µg Hb/g faeces had a risk of 2.7%, leaving a higher risk population ≥100 µg Hb/g faeces with a risk of 14.5%. An intermediate range of 10–149 µg Hb/g faeces resulted in an intermediate population risk of 3.2%, meaning all patients ≥10 µg Hb/g faeces would qualify for urgent investigation. The cancer risk for the intermediate 7–199 µg Hb/g faeces population was 2.8% with a risk of 17.2% in the ≥200 µg Hb/g faeces group. However, there was no intermediate population ≥20 µg Hb/g faeces with a risk below 3%. The patients with FIT ≥20 µg Hb/g faeces comprised 16.8% of the population tested compared with 21.9% for ≥10 µg Hb/g faeces and 25.4% for ≥7 µg Hb/g faeces.

Individualised FIT thresholds

All dichotomous FIT thresholds, from the LoD upwards, identify a population with CRC risk ≥3% as recommended by NICE for urgent referral. For example, the PPV for ≥2 µg Hb/g faeces was 4.7% (4.0% to 5.5%) in the Oxfordshire Primary Care cohort, rising to 8.4% (7.1% to 9.9%) using ≥10 µg Hb/g faeces.[23] An analysis from the Southwest of England discussed moving from population risk to individual risk.[11] The cancer risk in the ≥10 µg Hb/g faeces population was 7%, in line with larger data sets from low prevalence primary care populations.[18 23 26 27] Although cautious about the uncertainty in their estimate, they calculated that the individualised risk was 3% at the threshold ≥37 Hb/g faeces (95% CI 26 to 50) suggesting safety netting may be warranted between 10 and 36 Hb/g faeces.

SHOULD FIT BE USED IN PRIMARY OR SECONDARY CARE?

We recommend that FIT should be used by primary care clinicians to prioritise patients with clinical features of CRC for referral for urgent investigation.

GRADE of evidence: very low; Strength of recommendation: Strong.

There are no controlled studies or economic evaluations that compare the effectiveness of pathways using FIT in primary care with pathways using FIT in secondary care.

FIT in primary care: pre-referral

Four large retrospective cohort studies, in which not all individuals are investigated but have been followed-up, have described FIT usage for symptomatic patients in primary care: Northern Spain (n=38 675),[21] Oxford (n=16 604),[20] Tayside (n=5372)[16] and Nottingham (n=24 855)[10] where palpable rectal mass and bleeding were excluded.

In these large low prevalence cohorts, the cancer diagnosis rate at follow-up after reassurance without investigation based on very low fHb levels in primary care was 0.3% or less, regardless of variations in the platforms and cut-offs used. A further Danish study of 3462 patients evaluated FIT in patients without 'alarm symptoms' similarly found that the risk of CRC was <0.1% in those with fHb <10 µg Hb/g faeces.[13]

Evidence from these studies also demonstrates that primary care clinicians will still refer patients to secondary care where clinical concern persists via appropriate or alternate pathways. Unpublished data from Nottingham suggests one in three patients are seen in an alternate pathway after 'negative' FIT. One in seven FIT below the threshold patients were investigated in Denmark. A study from Southwest England,[11] reported that GPs made a referral within 3 months for 1 in 10 negative FITs

detecting more than half of the FIT below the threshold CRCs (5 of 8).

Some, not all, of these populations were included in a pooled analysis of 15 studies including 48 872 patients,[26] yielding a sensitivity for CRC of 87.2% (95% CI 81.0% to 91.6%) when using a threshold of ≥10 µg Hb/g faeces. A threshold of ≥20 µg Hb/g faeces missed less than one additional CRC per 1000 patients (from a population of five studies; n=24 187, with CRC prevalence 2%).

FIT in secondary care: post-referral

Large UK cohort studies of patients preselected for referral by GPs describe the performance of FIT in populations with the majority fulfilling 'high-risk' NG12 criteria all receiving colonic investigation.

The NICE FIT study,[28] a multicentre double-blinded study of 9822 patients undergoing colonoscopy, demonstrated that the risk of bowel cancer was around 0.2% in those with undetectable levels of fHb and 0.4% in those with fHb <10 µg Hb/g faeces. The Fast Track FIT study[29] evaluated 5040 patients undergoing colonoscopy, CTC or colorectal telephone assessment pathway showed the risk of bowel cancer was 0.4% in undetectable fHb and 0.5% in those with fHb <10 µg Hb/g faeces. The quantitative FIT (qFIT) study[30] reported on 3596 patients who underwent colonoscopy or CTC and the risk of CRC was 0.4% in those with undetectable fHb and 0.5% in those with fHb <10 µg Hb/g faeces. FIT kits were provided to patients in both primary care and hospital settings. A Scottish study of 4841 referred patients reported the risk of CRC when fHb <10 µg Hb/g faeces was 0.6%.[31]

Overall, this evidence suggests that FIT has an acceptable miss rate whether used in primary care prior to referral or in secondary care following referral.

FIT in primary care vs no FIT

A service evaluation from Nottingham including 1668 patients provides a small real-life uncontrolled comparison of an NHS Trust that adopted FIT for symptoms (excluding rectal bleeding and palpable rectal mass) covering half of the regions urgent 2WW CRC referrals and a private provider for the remainder of the referred population.[9] FIT rollout increased 2WW referrals and the proportion of new CRC diagnoses made on 2WW pathways. Emerging differences were noted in the cost of investigations required to detect each CRC and the time to diagnosis favouring the pathway using FIT.[32] Other regions of the East Midlands have restricted FIT usage to those over 60 years and demonstrated demand reduction[14] similar to the experience in Scotland where the introduction of FIT achieved a 15% reduction in urgent referrals from primary care.[16]

In Northern Spain[33] the clinical outcomes of 279 patients with symptomatic CRC diagnosed after a 'positive' FIT in primary care were compared with 1210 patients with symptomatic CRC without a primary care FIT. A higher proportion of Stage I and II cancers (51.3% vs 45.5%) and improved 3-year survival were found in the FIT group. The Nottingham group[9] reported a pre-pandemic shift towards diagnosis at earlier stage. Juul *et al*[13] report 66.7% of cancers diagnosed at Stages I and II when evaluating FIT in symptomatic patients without 'alarm symptoms'. Bailey *et al*[10] found 33% were detected at early stage when using FIT in those that satisfied DG30 criteria specifically. Turvill *et al*[29] described a higher proportion of Stage I and II CRC (52.7%) in their referred Fast Track study population with low fHb <18 µg Hb/g faeces although numbers are very small. Other studies have shown obstructing tumours and higher stage CRC are also common in FIT 'negative' CRC.

It is not possible to conclude that introducing FIT in primary care improves longer-term outcomes, but evidence is emerging that FIT testing in primary care could have this impact.

FIT only in secondary care

During the pandemic FIT was adopted widely across the UK given fears that endoscopy and CTC were aerosol generating procedures that increased risk of viral transmission.[18] High fHb thresholds (100 µg Hb/g faeces in England and Wales, 400 µg Hb/g faeces in Scotland) were recommended with a pragmatic acceptance that some diagnoses would be missed, and a number of reports have described this.

High fHb could be used to identify referred patients for urgent/2WW/direct to colonoscopy pathways, with lower fHb directed to routine pathways. FIT could be used to 'upgrade' patients referred routinely and fHb might be used to determine the choice between colonoscopy and CTC, or colonoscopy and flexible sigmoidoscopy. An fHb could also become a component of all informed consent conversations for invasive colonic investigation. The current statute law underlying the 2WW system and the timed nature of pathways inhibits this individualised approach. 'Local agreement' is key to best practice in implementation.

It has been suggested that access to FIT should be restricted for use in secondary care but studies describing a favourable stage shift associated with FIT use suggest that a secondary care only approach may miss the opportunity to increase the proportion of cancers detected by identifying higher risk patients before referral.

ADVICE FOR CLINICIANS WHERE PATIENTS HAVE NOT RETURNED AN FIT TEST

We suggest that clinicians should follow-up patients with no FIT result to encourage them to return a sample or, where the kit has been lost or inadequately submitted, offer a further test.

GRADE of evidence: very low; Strength of recommendation: weak.

We suggest that patients who decline to return an FIT test should be counselled that evaluation of their symptoms is incomplete, and be encouraged to complete their test.

GRADE of evidence: very low; Strength of recommendation: weak.

We suggest that where no FIT result can be obtained, clinicians should use existing national and local guidelines to assess risk of CRC.

GRADE of evidence: very low; Strength of recommendation: weak.

There is very limited evidence on how to manage patients who do not return and/or refuse to undertake an FIT test, however we have sought to develop relevant advice for clinicians.

There is limited survey evidence that most patients find FIT testing acceptable but that people from ethnic minorities may be less likely to return kits possibly due to concerns about hygiene.

There are a few studies suggesting possible interventions that may improve rates of return of FIT kits. In the absence of abdominal or rectal mass or ulceration, FIT is the best discriminator of a patient's risk and need for referral to investigate possible CRC.

Importance of FIT testing

Numerous studies and reviews have found strong associations between an FIT positive test and risk of CRC. Studies that

compared the strength of this association with other risk factors have shown that a positive FIT test is usually more predictive of risk than demographic, clinical and laboratory criteria for referral to investigate possible CRC.[28 34–36]

Improving return of tests

A small number of articles were identified that provide insights into strategies for maximising return of FIT kits in patients who have been asked to have the test.

Coronado *et al* undertook surveys on worded versus non-worded instructions for performing FIT testing in an area with a population having high rates of non-English speakers. They reported preferences for non-worded instructions from both patients and professionals.[37]

A US study of FIT used for screening found that patients asked to complete a two-sample test were less likely to return than those completing a one-sample test; this difference was statistically significant though not numerically large (39.6% vs 43.3%).[38]

Haghighat *et al* described an initiative to encourage patients to submit their FIT kit as part of colorectal screening as soon as possible after this was offered, ideally before leaving the clinic. They reported significant improvements over the 6-month period of study (27.6% v. 20.6%, p<0.001).[39]

A survey of patients in the NICE FIT study examined 1151 questionnaires representing 30.6% of those mailed out (1151/3760), with lower percentage returns from London than outside London patients (17% and 43%, respectively). Most patients found FIT collection straightforward (90.2%), not unhygienic (76.3%) and preferable to colonoscopy (78.1%). People aged 40–64 years were less likely to prefer FIT to colonoscopy than older age groups. Patients from ethnic minority backgrounds were less likely to have found the test hygienic and to return the kit in a future test.[40]

SAFETY NETTING

We recommend that some patients with symptoms of suspected CRC may be managed in primary care if fHb <10 μg Hb/g, and provided appropriate safety netting is in place

GRADE of evidence: very low; Strength of recommendation: strong.

We suggest that patients with an fHb <10 μg Hb/g but with persistent and unexplained symptoms for whom the GP has ongoing clinical concern should be referred to secondary care for evaluation.

GRADE of evidence: very low; Strength of recommendation: Strong.

We recommend that safety netting protocols should incorporate advice and strategies for the diagnosis of CRC and extracolonic cancer, as well as other serious gastrointestinal conditions.

GRADE of evidence: very low; Strength of recommendation: weak.

Most patients with symptoms and signs suggestive of CRC may be managed in primary care if the FIT level is low or undetectable. The risk of CRC in patients with fHb <10 μg/g of faeces approximately equates to the risk of severe complications from colonoscopy, or to the CRC risk in asymptomatic subjects. GPs may consider alternative causes for abdominal symptoms if FIT testing is below the threshold for referral, given the absolute risk of CRC is low in this situation. Where the primary care clinician has ongoing concerns about a serious cause, they should consider non-GI as well as GI conditions, including cancers not located in the colon or rectum. There appears to be a limited role for other tests such as a full blood count (FBC), combined with persistent symptoms and/or clinical acumen, to determine which patients with a negative FIT result may be considered at increased risk of CRC, and further work may be required to identify robust safety netting mechanisms which could be employed. However there will always remain an important role for clinical acumen and personalisation of care for patients who may be managed in a myriad of different ways for very different symptoms, and who may refer on alternate pathways, or managed in primary care accordingly (figure 1).

Safety netting

Safety netting has come to be regarded as 'best practice' in relation to cancer diagnosis, especially in non-specialist settings.[41 42] Its aim is to ensure patients do not drop through the healthcare net but are monitored until symptoms are explained, defined as a consultation technique to communicate uncertainty, provide patient information on red-flag symptoms and plan for future appointments to ensure timely re-assessment of a patient's condition.[43] NICE refer to safety netting as 'the provision of support for patients in whom the clinician has some uncertainty as to whether the patient has a self-limiting illness and is concerned that their condition may deteriorate'.[6] However, safety netting may also comprise administrative activities such as test result reconciliation and the follow-up of referrals.[44 45] A key role for safety netting in FIT based pathways is the monitoring of FIT negative patients to ensure timely referral or investigation of those referred.

Absolute risk of missed cancers

In a recent meta-analysis pooling data from 35 925 patients from nine UK studies from primary and secondary care including a range of FIT thresholds from ≥2 to ≥19 μg Hb/g faeces and within the NICE NG12 context, the pooled percentage of missed CRCs due to an FIT below the selected threshold was 8.7% (95% CI 5.1% to 12.2%) equating to an NMC of 2.1 per 1000 patients tested.[46] Pin-Vieito *et al* reported the NMC as 1 per 1000 patients tested at a CRC prevalence of 1% and 3 in 1000 at a prevalence of 2%, using a threshold of ≥10 μg Hb/g faeces, noting that the prevalence of CRC in primary care based studies ranged from 0.8% to 1.8%.[26] Risks of 1 and 3 per 1000 patients equate to absolute cancer risks of 0.1% and 0.3%, respectively, both significantly below the current NICE threshold of ≥3% cancer risk used to warrant urgent cancer investigation.[47] An effective safety netting strategy could identify FIT negative patients with an increased risk of cancer who may warrant further investigation.

Meta-analyses and randomised controlled trials

We found no meta-analyses or RCT of safety netting strategies to ensure CRCs are diagnosed in patients with a negative FIT, in primary or secondary care settings. A step-wedged cluster RCT is currently underway to test the effectiveness of an electronic safety netting toolkit embedded into major primary care clinical systems to facilitate patient follow-up in terms of the time and route to diagnosis.[48]

Observational studies

There were no observational studies evaluating safety netting strategies to promote re-consultation and onward referral among people with ongoing symptoms despite a negative FIT result.

Recent research has emphasised the importance of clinician 'gut feeling' in the diagnosis of cancer, conceptualised as the

rapid summing up of multiple verbal and non-verbal patient cues.[49] FIT pathways should allow clinicians to refer or investigate FIT negative patients if there are ongoing clinical concerns. In a cohort study from the Southwest of England, GPs still requested urgent investigation for five of the eight FIT negative cancers 'probably because continuing symptoms allowed the GP to 'overrule' the negative test'.[11]

A common suggestion in the literature and guidelines was re-consultation within 4–6 weeks for patients with ongoing symptoms and an FIT below threshold. G27 guidance (2005), later replaced by NG12, recommended urgent referral for patients with symptoms persistent for 6 weeks. Underpinning evidence to inform the timing of any safety netting action is lacking including: what might be considered the 'normal' duration of a benign symptom, the time taken for progression of high-risk adenomas to cancer, or the interval of stage progression.

Many cohort studies have documented the clinical presentation of patients later diagnosed with FIT negative CRC, suggesting that these characteristics could be prioritised for referral or included in the communication of safety netting advice to patients.[16 27 50 51] However, there is marked variation in the characteristics of FIT negative cancers between these studies and so relying on these characteristics to inform a safety netting strategy could be falsely reassuring.

Modelling studies

Modelling studies to date have not demonstrated the benefit of combining FIT with other clinical features and blood test results to enhance sensitivity by reducing false negative FITs. A comparison of FIT at ≥10 µg Hb/g faeces alone, with the FAST score (combining FIT age and sex), and ColonFlag (a machine learning algorithm using age, sex and FBC indices to derive a risk score), showed that FIT and ColonFlag missed a different 18% of CRCs, respectively, and FAST score missed 27.3%.[52] Combining simple blood tests with FIT at best matches the sensitivity of FIT alone in patients tested in primary care, whether as pairs of results or within multivariable model.[20]

IS A REPEAT/SECOND FIT USEFUL AND DOES IT ENHANCE DIAGNOSTIC ACCURACY?

Studies suggest repeat FIT testing may enhance sensitivity, but lower specificity, and this depends on whether the second test is used to identify people to be investigated/referred after the first test is negative (increased sensitivity and decreased specificity) or to identify people who may not need referral unless both tests are positive (decreased sensitivity and increased specificity). Studies have examined cohorts identified for investigation (or already investigated/diagnosed) rather than prospectively using FIT to guide referral in 'real world' situations. Although the populations under study have varied considerably (symptomatic vs screening; high vs low risk) the findings of sensitivity and specificity have been relatively consistent. No studies were found that examined the optimal period for undertaking a repeat/second FIT test. Where it was clear in the methods, most studies instructed repeat FITs to be sampled from consecutive stools. In conclusion, although there is currently insufficient evidence to recommend use of repeat/second FIT to guide referrals in routine practice, further data are required to clarify the role of this approach (online supplemental file 2).

There have been no randomised controlled trials or systematic reviews comparing diagnostic yield, time to diagnosis, stage at diagnosis or longer-term CRC outcomes between patients who have one and those having repeat/second FIT tests. Mosen *et al*[38] conducted an RCT of 3121 participants comparing uptake of a two sample regimen (1562) with one sample FIT (1559). Participants were given the same instructions with the 2-FIT group required to do the test twice. The FIT was requested in the context of bowel cancer screening. No significant difference in the baseline characteristics of each group. The FIT kits were posted to the participants and returned by mail. A total of 43.3% of the 1-FIT group were compared with 39.6% (p=0.012) of the 2-FIT group. In a large systematic review summarising the diagnostic performance of FITs for CRC including 69 536 symptomatic adults from primary care including 23 cohort studies, where studies included findings from patients tested more than once, only the first FIT result was analysed.[1] Therefore the predominant evidence source is observational.

Turvill *et al*[53] undertook a prospective, blinded observational study of associations between FIT results from two samples in all patients referred to York Hospital with suspected CRC within the urgent (2WW) pathway from February 2016 to March 2017. The FIT samples were provided by the patients between the hospital clinical appointment and investigations in secondary care. For patients with a single positive FIT, a threshold of ≥10 ug/g, was associated with sensitivity of 84.6% and specificity of 88.7%. For patients with two positive FIT tests, sensitivity was 91.7% and specificity of 85.1%. The paper did not examine and compare sensitivity and specificity in patients who were only offered one FIT test. Nor did it report on the negative predictive value (NPV) of two versus one FIT <10 ug/g.

Hunt *et al*[54] examined the association between CRC diagnosis and FIT results in patients who had two FIT following a referral to a specialist service from 2017 to 2021.[12] Patients had been referred under different clinical pathways at different times, specifically at times under a low-risk versus high-risk pathway. The patients were asked to return two FIT kits from different stools before clinical assessment in secondary care. They found that if patients had been referred based on FIT result, sensitivity for CRC would have been 97.8% and 91.5%, specificity 66.2% and 81.6% and PPV 3.1% and 5.2% with one or two FIT positive test results (>10 ug/g), respectively. Two tests were returned by 96.1% of the study population indicating the data were representative of the study population. Those studied were initially those referred with low-risk symptoms and later those with high-risk symptoms. Missed CRC detection with two FIT <10 was found in 7/73 (9.6%). All the patients with 'missed' cancers had anaemia and one had an obstructing tumour.

This study provides evidence that a requirement to test positive (FIT >10 ug/g) twice rather than once before decision to refer, or to investigate post-referral, may reduce the numbers of people referred or investigated, respectively, though at the cost of missing a proportion of CRC cases. The experience may not directly test real-world practice however where those with one or even two negative tests may still be referred and/or investigated if there remain clinical concerns.

Mattar *et al* studied 289 patients who underwent colonoscopy who had been entered into either a one-sample or two-sample FIT protocol.[55] It is not clear from the description if patients selected were from a symptomatic or screening population. Among them 172 had one-sample FIT; for these positive and negative rates were not reported but colonoscopy outcome findings were reported in 99 cases and 117 people received the 2-sample FIT and of these 94 (80.3%) patients had both FIT below the threshold, 13 (11.1%) had both FIT positive and 10 (8.5%) had only one FIT positive (≥10 ug/g). For the one-sample FIT group, positive FIT had a sensitivity and specificity of 83.3% and 86.9%, respectively. For the two-sample group,

those who had at least one sample positive had sensitivity and specificity of 75% and 92.9%, respectively. Separate figures for those who had two versus one sample positive in the two-sample group were not provided in the text.

Observational studies comparing the use of one and two FITs in bowel cancer screening reveal increased PPV for CRC and high-risk polyps. Moosavi *et al*[56] reviewed 17 031 participants in the British Columbia screening programme. The PPV following two positive FITs (at a cut-off of 20 ug/g) was 8% versus 1% for one positive FIT. For high-risk polyps the PPVs were 40% and 20%, respectively. CRC and high-risk polyps were missed with one FIT specimen. Polyps amounting to 12.1% of cancers and 23.4% were identified in patients where the first FIT was negative and the second positive.

Lim *et al*[57] retrospective study of 1672 participants from Singapore's bowel cancer screening programme found one FIT cohort had significantly less cases of CRC and polyps found than in the two FIT group. Both these studies asked patients to sample stools on consecutive days. As investigation of the bowel in these studies is only triggered by an FIT result over the threshold, the negative predictive of two FIT compared with one is not known.

In a population-based case–control study, Kim *et al*[58] examined the associations between previous colonoscopy and FIT testing, and the risk of future CRC diagnosis by comparing data from 61 221 patients with newly diagnosed CRC (case group) and 306 099 individuals without CRC (control group). Data on testing and diagnosis were from claims data from the Korean National Health Insurance System. They found that previous FIT testing was associated with lower OR for CRC, but where patients had records of >1 previous FIT ORs successively increased. FIT testing may have largely reflected screening so may not be applicable to use in symptomatic patients. Where symptoms based, repeat testing may reflect the presence or persistence of concerning symptoms rather the utility of repeat testing.

Maeda *et al*[59] evaluated the impact of using one versus two FIT tests (using ≥10 ug/g threshold) to guide specialist investigation by modelling in a COVID-19 adapted pathway. The study also examined the impact of CT mini-prep. Values for FIT sensitivity and specificity used in the analysis were derived from audit data, South East *Scotland* Cancer Network data, literature and, if missing, assumptions on reasonable (best-versus-worst-case) scenarios were made by expert opinion. Sensitivity (84%) and specificity (74%) figures were broadly in keeping with those reported by cohort studies. The modelling estimated that investigating all patients with any positive FIT result out of two would reduce the risk of missing a CRC from 20.2% to 15.5%, identifying 13.3 versus 10 patients per 1000 patients referred on a non-FIT pathway, while increasing the numbers investigated from 287 to 359 per 1000 patients on the referral pathway. This is compared with fewer than 5% missed CRC (3 per 1000) on the pre-COVID pathway.

The COLONFIT study[60] developed a scoring system to prioritise fast-track colonoscopy. They obtained three FIT samples from 1495 patients with symptoms (1058 met NICE NG12 guidelines) diagnosing 116 CRC. 6/116 (5%) had only 1/3 FIT >11, 3 CRC patients (2.6%) had negative FIT <4 and 2 patients were >4 ug/g and <11 ug/g.

DIAGNOSTIC ACCURACY OF FIT FOR CRC IN PEOPLE WITH SUSPECTED CRC SIGNS OR SYMPTOMS

FIT is a triage tool to identify those patients with symptoms of suspected CRC who should undergo further colorectal investigation.

Table 1 Number needed to scope (NNS) to detect one cancer and number of missed cancers (NMC) per 1000 faecal immunochemical tests (FITs) at various thresholds of FIT[17]

Threshold (µg Hb/g faeces)	Positive FITs n (%)	Negative FITs n (%)	Cancers detected n (%)	NNS to detect one cancer	NMC per 1000 FITs
≥7	111 (11)	889 (89)	10 (91)	11	1
≥10	96 (10)	904 (90)	10 (91)	10	1
≥20	71 (7)	929 (93)	9 (85)	8	2
≥50	44 (4)	956 (96)	8 (74)	6	3
≥100	30 (3)	970 (97)	7 (61)	5	4
≥120	28 (3)	972 (97)	6 (57)	5	5
≥150	25 (2)	975 (98)	6 (54)	4	5

GRADE of evidence: low; Strength of recommendation: strong.

We suggest that FIT be used for people with iron deficiency anaemia within primary care to inform urgency of referral.

GRADE of evidence: low; Strength of recommendation: weak.

We suggest referral of patients with persistent/recurrent anorectal bleeding for flexible sigmoidoscopy if fHb <10µg Hb/g.

GRADE of evidence: very low; Strength of recommendation: weak.

In summary, a meta-analysis informing these guidelines[61] and four prior meta-analyses of over 48 000 patients, which include the largest three studies from NICE FIT, qFIT and the York groups on FIT diagnostic accuracy reported an FIT sensitivity for CRC in symptomatic patients to be greater than 87% at a threshold of 10 µg/g[28 29 62] (table 1). Therefore, based on the studies reviewed in this section, FIT should be considered in patients presenting with lower GI symptoms irrespective of their nature, to support referral or triage to appropriate investigations if there are concerns about a cancer diagnosis.

Introduction

Considerable emerging evidence has recently been published on the diagnostic accuracy of FIT in symptomatic patients using a range of thresholds.[26 63–66] The most common reported fHb triage threshold is 10 ug/g. Many of these reports assessed all patients presenting to their primary care practitioners with any bowel symptoms suspicious of CRC, but others categorised symptoms into low and high risk symptoms as defined by NICE.[67] Only a few studies examined the diagnostic accuracy of FIT for individual symptoms.

In this section we a focus on those studies where all symptomatic patients that received FIT were linked with a reference standard investigation with full evaluation of the colon and rectum to exclude CRC with either colonoscopy or CTC. Where these evaluations were not performed, studies with other reference standards such as flexible sigmoidoscopy or CT scan and those with clinical follow-up/record linkage of a minimum of 3 months were examined. Where this was not available then studies with lesser follow-up and other linked investigations such flexible sigmoidoscopy or CT scan were included. In assessing the diagnostic accuracy of FIT we considered its accuracy in symptomatic patients in general, and also in 'high-risk' and 'low-risk' symptoms.

Early studies (table 2)

One of the first studies to examine the role of FIT in symptomatic patients was published in 2011 by a Dutch group who

Table 2 FIT diagnostic accuracy for CRC at a cut-off of 10 µg/g in the early diagnostic accuracy studies prior to 2017

	Region	Design	n	Analyser	Reference standard	CRC sensitivity @ 10 µg/g	CRC specificity @ 10 µg/g	CRC PPV @ 10 µg/g	CRC NPV @ 10 µg/g
Terharr sive Droste *et al*[144]	Holland	DTA	2058	OC-Sensor	Colonoscopy	91.1% (84.2% to 95.6%)	87.0% (85.4% to 83.5%)	–	99.4% (98.9% to 99.7%)
McDonald *et al*[68]	UK (Scotland)	DTA	280	OC-Sensor	Colonoscopy	100% (54.1% to 100%)	93.8% (90.3% to 96.3%)	–	100% (98.5% to 100%)
Rodríguez-Alonso *et al*[145]	Spain	DTA	1003	OC-Sensor	Colonoscopy	96.7% (82.8% to 99.9%)	79.9% (77.2% to 82.3%)	12.8% (9.1% to 17.9%)	99.9% (99.3% to 100%)
Mowat *et al*[64]	UK (Scotland)	DTA	750	OC-Sensor	Colonoscopy	89.3% (71.8% to 97.7%)	79.1% (75.9% to 82.0%	14.2% (9.8% to 20.1%)	99.5% (98.5% to 99.8%)
Godber *et al*[70]	UK (Scotland)	DTA	484	HM-JACKarc	Colonoscopy	100% (71.5% to 100%)	76.6% (72.6% to 80.3%)	9% (5.1% to 15.4%)	100% (99.0% to 100%)

95% CIs given in brackets when reported.
CRC, colorectal cancer; DTA, diagnostic test accuracy study; FIT, faecal immunochemical testing; NPV, negative predictive value; PPV, positive predictive value.

conducted a clinical study involving five centres testing FIT in a mixed cohort of symptomatic and asymptomatic patients who were scheduled for colonoscopy. A total of 2145 patients undifferentiated by colonoscopy indication were included which were then divided irrespective of their symptoms or lack of, into high and low risk groups for CRC. The overall sensitivity and specificity of FIT for CRC was 92.4% (95% CI 84.2% to 97.2%) and 86.4% (95% CI 84.8% to 87.9%).[68] In 2013, the Tayside group in 2013 examined 280 participants who had both FIT and colonoscopy and found that patients with cancers had a median fHb of >1000 ng Hb/mL buffer (equivalent to >200 ug/g). Using a cut-off fHb concentration of 50 ng Hb/mL buffer (equivalent to 10 ug/g), the NPV for CRC was 100%. A year later the same group reported similar results but on a larger number of patients (n=569) and concluded that using FIT in primary care may help target colonoscopy more appropriately when patients present with colorectal symptoms.[69] The same year, a group from Spain compared FIT with NICE 2005 and the Scottish Intercollegiate Guidelines Network (SIGN) referral criteria in 787 symptomatic patients FIT at >100 ng/mL (equivalent to 20 ug/g) had a higher sensitivity for CRC detection (87.6%) than NICE criteria (61.9%; p<0.001) and SIGN criteria (82.5%; p=0.4).[24] The specificity of FIT was also higher than NICE and SIGN criteria (77.4%, 65.2%, 42.7%; p<0.001). In 2016 the Tayside group reported on 755 patients with FIT and endoscopy results. The sensitivity and specificity at a cut-off of 10 ug/g was 89.3% (95% CI 71.8% to 97.7%) and 79.1% (95% CI 75.9% to 82.0%), respectively.[64] The same year another Scottish group reported on 484 patients who had FIT and colonoscopy and reported that all 11 cancers were detected at a cut-off of 10 ug/g (100% sensitivity).[70]

Later studies (table 3)

In 2017, NICE produced its DG30 guidelines which recommended the use of FIT in low-risk symptoms defined as 'patients without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer referral'.[5] The latter refers to high risk symptoms as defined in the updated NICE NG12 guidance in 2017[67] where use of FIT was not recommended. The DG30 guidance was based on a health technology assessment, commissioned by The National Institute for Health Research to produce a diagnostic accuracy report on FIT to triage symptomatic patients at low risk of CRC presenting in primary care.[63] The report looked at 10 studies but summarised evidence from 5 studies only that reported on FIT as a rule-out test for CRC with a cut-off of 10 µg/g. Data were taken from one study (507 patients) for the HM-JACKarc analytical system,[70] and four studies (4091 patients) for the OC-Sensor analyser.[64] The summary estimate of sensitivity for the HM-JACKarc was 100% (95% CI 71.5% to 100%) and for the OC-Sensor was 92.1% (95% CI 86.9% to 95.3%).[63] The corresponding specificity was 76.6% and 85.8%.

Table 3 Systematic reviews of FIT diagnostic accuracy for CRC at a cut-off of 10 µg/g in symptomatic patients

	Design	n	Analyser	Reference standard	CRC sensitivity @ 10 µg/g	CRC specificity @ 10 µg/g
Westwood *et al*[63]	SR	4091	OC-Sensor	Various	92.1% (86.9% to 95.3%)	85.8% (78.3% to 91.0%)
Pin Vieito *et al*[65]	SR	4035	OC-Sensor	Various	94.1% (90.0% to 96.6%)	66.0% (47.1% to 80.9%
Stonestreet *et al*[66]	SR	4096	OC-Sensor	Various	93%* (88% to 0.96%)	87%* (83% to 90%)
Pin Vieito *et al*[65]	SR	48 872	OC-Sensor/ HM-JACKarc	Various	87.2% (81.0% to 91.6%)	84.4% (79.4% to 88.3%)
Saw *et al*[71]	SR	25 500	OC-Sensor/ HM-JACKarc/ FOB Gold/ QuikRead Go	Various	88.7% (85.2% to 91.4%)	80.5% (75.3% to 84.8%)
Booth *et al*[61]	SR	35 945	OC-Sensor/ HM-JACKarc/ FOB Gold/ QuikRead Go	Colonoscopy and CT	91.0% (88.9% to 92.7%)	75.2% (69.6% to 80.1%)

95% CIs given in brackets when reported.
*10–15 µg/g.
CRC, colorectal cancer; CTC, CT colonography; FIT, faecal immunochemical testing; SR, systematic review and meta-analysis.

Two years later, a meta-analysis by the Warwick group included 17 studies of which 9 were on symptomatic cohorts (6755 patients).[66] Five studies used the OC-sensor (4883 patients), three used HM-JACKarc (1499 patients) and one used the Actim Faecal Blood system. Five Studies (4603 patients; four OC-Sensor and one HM-JACKarc) examined FIT at a cut-off of 10 ug/g and the others looked at a range of cut-offs ranging from 7 to 50 ug/g. The overall pooled sensitivity and specificity for CRC were 0.90 (95% CI 0.87 to 0.92) and 0.87 (95% CI 0.83 to 0.90), respectively.

A subanalysis for studies that used OC sensor was performed. These studies examined multiple cut-off concentration values ranging from 10 to 40 µg/g. Analysis of the pooled sensitivity and specificity for an fHb cut-off range of 10–15 µg/g (4096 patients) showed sensitivity of 0.93 (95% CI 0.88 to 0.96) and specificity of 0.87 (95% CI 0.82 to 0.90). For the range between 20 and 40 µg/g, the pooled sensitivity and specificity of 0.87 (95% CI 0.84 to 0.90) and 0.89 (95% CI 0.84 to 0.92), respectively.

In the same year, a meta-analysis from Spain by Pin Vieito included 14 studies of which 7 were on symptomatic cohorts.[65] Four studies (4035 patients) reported on FIT with a cut-off of 10 µg/g using the OC-Sensor; one of these studies was conducted in Scotland, and the others were conducted in Spain, or pooled data from studies from both countries. The pooled sensitivity for CRC was 94.1% (95% CI 90.0% to 96.6%) and specificity 66% (95% CI 47.1% to 80.1%).

A meta-analysis by the same group in 2021 included 23 studies (69 536 patients).[65] The meta-analysis examined diagnostic accuracy of FIT at different thresholds. Fifteen studies (n=48 872) reported on a cut-off of 10 ug/g. The pooled sensitivity and specificity for CRC was 87.2% (95% CI 81.0% to 91.6%) and 84.4% (95% CI 79.4% to 88.3%), respectively. Five studies (n=24 187) reported on a cut-off of 20 ug/g and the pooled sensitivity and specificity were 84.1% (95% CI 78.6% to 88.4%) and 86.6% (95% CI 75.6% to 93.1%). Six studies (n=34 691) assessed FIT as rule in test cut-off of >150 ug/g showing a sensitivity of 64.1% (95% CI 57.8% to 69.9%) and a specificity of 95.0% (95% CI 91.2% to 97.2%). The group concluded that FIT is the test of choice to evaluate patients with new-onset lower GI symptoms in primary healthcare.

The most recent meta-analysis published in December 2021 from New Zealand included 15 studies with a cohort of 28 832 patients, all of whom were prospectively recruited.[71] Thirteen studies (six HM-JACKarc, four OC-Sensor, one FOB Gold and two QuickRead Go analysers; n=25 500) reported on FIT at a cut-off 10 ug/g. The summary sensitivity and specificity were 88.7% (95% CI 85.2% to 91.4%) and 80.5% (95% CI 75.3% to 84.8%), respectively. At the lower cut-off of the LoD (three studies; 15 160 patients), the summary sensitivity increased to 96.8% (95% CI 91.0% to 98.9%) but specificity reduced to 65.6% (95% CI 59.0% to 71.6%).

A meta-analysis performed to inform these guidelines included 31 studies up to March 2022 with a cohort of 79 566 patients. For 'all symptoms', 'all analyser' analysis and a reference standard of >90% receiving either colonoscopy or CTC (16 studies, n=35 945), the summary sensitivity and specificity were 91.0% (95% CI 88.9% to 92.7%) and 75.2% (95% CI 69.6% to 80.1%), respectively, at a cut-off 10 µg/g.[61]

In the 2 years between the 2019 and 2021 meta-analyses, there has been an explosion in the number of studies reporting on FIT, with between 25 000 to 40 000 patients added to the latest meta-analyses.[61] The Pin Vieito and Saw meta-analyses included two of the three largest diagnostic accuracy, multicentre studies that were conducted in England.[28 62] The qFIT study (UCLH Cancer Collaborative) included 3596 patients with high-risk symptoms and reported a sensitivity of FIT for CRC at 83.3% (95% CI 75.6% to 91.0%) at cut-off of 10 µg/g using the OC-Sensor.[62] The NICE FIT study included 9822 patients with high and low risk symptoms and at the same cut-off, reported a sensitivity for CRC of 90.9% (95% CI 87.2% to 93.8%).) using the HM-JACKarc analyser.[28] The third largest research study published in 2021 by the York group included 5040 patients with high-risk symptoms and was included in a meta-analysis to inform these guidelines.[29 61] The sensitivity and specificity of FIT for CRC at 10 ug/g using the HM-JACKarc analyser was 87.4% (95% CI 81.0% to 92.3%) and 80.9% (95% CI 79.7% to 81.9%), respectively. The group considered an optimal threshold between sensitivity and specificity and calculated this at 19 ug/g with a sensitivity of 85.4% (95% CI 78.8% to 90.6%) and specificity of 85.2% (95% CI 84.1% to 86.2%).

High and low risk symptoms

Low risk

Up until NICE released its DG30 guidelines, most studies investigated FIT in patients that presented to clinicians with bowel symptoms that required investigations to rule out bowel cancer. Indeed, DG30 was based on studies that included patients with wide-ranging symptoms, not stratified by high or low-risk symptoms in accordance with NICE criteria.

Since then, many studies began to report on low-risk and high-risk symptoms. There are a small number of studies investigating low risk symptoms presenting to primary care. The largest studies included three service evaluations[11 13 19] and one diagnostic accuracy study.[72] The service evaluations are not true diagnostic accuracy but are pragmatic studies reflective of what happens in real-life practice in that not all patients receiving FIT undergo investigations and those investigated may not necessarily receive full colonic imaging such as in elderly and/or unfit patients who may have a CT scan or flexible sigmoidoscopy instead.

Juul in 2018 investigated FIT at a cut-off of 10 ug/g in patients presenting with non-alarm symptoms in general practice in a Central Denmark Region.[13] In total 3462 patients had FIT and of these, 540 (15.6%) were positive. Of these, 416 patients (77%) underwent diagnostic investigation within 3 months and 51 cancers (PPV: 9.4% (95% CI: 7.0% to 11.9%)) were found. Of the 2922 patients with FIT below 10 ug/g only 418 (14.3%) underwent a diagnostic investigation during the same period and three cancers were found.

The same year Nicholson *et al* reported on 238 patients with low-risk symptoms in Oxfordshire who had both faecal occult blood test and FIT and were followed-up for up to 21 months.[19] The sensitivity and specificity of FIT at 10 ug/g were 85.7% and 89.2%, respectively. The PPV was 19.4% and NPV was 99.5%.

Bailey in 2021 reported on FIT at a cut-off of 10 ug/g in 3890 patients presenting in primary care in the Southwest of England with low-risk symptoms.[11] Of these, 618 (15.9%) patients tested positive and were referred for investigations within 12 months and 43 were diagnosed with CRC (PPV 7.0% (95% CI 5.1% to 9.3%)). Of 3272 with FIT <10 ug/g, 324 (9.9%) were referred and in these 5 had CRC within 12 months. Of those 2948 patients who were not referred within 12 months, 3 had cancers. NPV was 99.8% (CI 99.5% to 99.9%). Sensitivity was 84.3% (95% CI 71.4% to 93.0%) and specificity was 85.0% (95% CI 83.8% to 86.1%).

The NICE FIT study reported on 1994 patients (20.3%) of the 9822 patients studied who had low-risk symptoms and 634 (6.5%) had other symptoms warranting urgent referral.[72] The

sensitivity of FIT for CRC at thresholds of 2 and 10 ug/g were 94.3% (95% CI 84.3% to 98.8%) and 86.8% (95% CI 74.7% to 94.5%). The PPV for CRC at the same thresholds were 8.4% (95% CI 6.3% to 10.9%) and 16.9% (95% CI 12.7% to 21.9%). NPV were 99.8% (95% CI 99.4% to 100%) and 99.6% (95% CI 99.2% to 99.8%), respectively. Even in patients with other symptoms which did not meet NICE referral criteria but were referred because of general practitioners' concerns, FIT sensitivity and specificity for CRC was 84.2% (95% CI 60.4% to 96.6%) and 82.6% (95% CI 79.4% to 85.5), respectively.

In a meta-analysis developed to inform the guidelines,[61] three studies (n=2161), that used the DG30 definition of symptomatic patients and applied colonoscopy or CTC as the reference standard were identified.[51 72 73] The summary sensitivity and specificity estimates were 88.7% (95% CI 78.1% to 95.3%) and 88.5% (95% CI 87.1% to 89.9%).

High risk

There are a larger number of studies evaluating high-risk symptoms which are summarised below (table 4). Most of these studies categorise patients according to NICE 2017 criteria. The three largest diagnostic accuracy studies in England included high-risk symptoms in over 15 000 patients.[28 29 62] In addition, service evaluation from Nottingham,[74] Tayside, Scotland,[64] Oxfordshire[27] and San Sebastian region in Spain[21] have reported on high-risk symptoms although the Tayside group do not categorise as per NICE criteria because they are not applicable in Scotland. These studies report a sensitivity ranging from 83% to 91%.

However, the rule out or NPV of FIT for CRC in symptomatic patients meeting 2WW criteria in the UK is consistently above 98.5%; in the largest studies, it was 99.5%–99.6%. This means that in symptomatic patients with an fHb of <10 µg/g, the chance of having a cancer is 0.5% and the number needed to investigate/scope to detect one cancer would be over 200. This is compared with 6–10 patients with an fHb above 10 µg/g.

A meta-analysis to inform the guidelines identified seven studies (n=18 264) that used the NG12 definition of symptomatic patients and colonoscopy or CTC as the reference standard.[14 51 62 72 75–77] The summary estimates of sensitivity and specificity were 88.7% (95% CI 84.4% to 92.0%) and 78.5% (95% CI 73.0% to 83.2) at a cut-off of 10 µg/g.

Specific symptoms

Although NICE has recommended in DG30 guidance use of FIT to triage low risk symptoms in primary care, it excluded patients with rectal bleeding from FIT testing.[5] Moreover, early diagnostic accuracy and service development studies have recommended exclusion of certain symptoms from FIT testing including patients with rectal bleeding on the assumption of a high false positive rate. Patients with iron deficiency anaemia (IDA) or palpable abdominal mass were excluded after smaller studies reported false negative rates (undetected cancers) in patients meeting these symptoms. However, recent studies have confirmed that FIT can be used in specific high-risk symptoms, including IDA, rectal bleeding, and abdominal masses.

Rectal bleeding

There are several studies that reported on use of FIT in symptomatic patients with higher risk symptoms, including patient cohorts with rectal bleeding.[16 27 31 78] However, three studies have focused solely on use of FIT in patients with rectal bleeding.[17 77 79]

The use of FIT in rectal bleeding was investigated recently in 462 patients in NHS Tayside, Scotland.[17] The positivity rate was 63.3% at a cut-off of 10 µg/g. The prevalence of cancer was 8.5% (25/293) with an fHb >10 ug/g compared with 0.6% (1/168) when fHb <10 ug/g. The sensitivity and specificity for CRC is calculated as 96.2% (95% CI 80.4% to 99.9%) and 38.3% (95% CI 33.7% to 43.0%), respectively. The one CRC in the cohort with an fHb <10 ug/g was in the descending colon and would have been detected by flexible sigmoidoscopy. Indeed, flexible sigmoidoscopy detected the majority of serious bowel disease (SBD) pathology (CRC, inflammatory bowel disease and advanced adenomas) except for four advanced adenomas (10 out of 14 SBD out of 168 patients). The authors concluded that patients with an fHb <10 ug/g and persistent rectal bleeding, can be safely investigated with flexible sigmoidoscopy.

Högberg *et al* in 2020 reported on qualitative (using three FIT samples) rather than quantitative FIT in 606 patients with rectal bleeding.[79] The positivity rate was 42% with a sensitivity of 96.2% and NPV of 99.7% for CRC.

The NICE FIT study investigated the diagnostic accuracy of FIT in 3143 patients with rectal bleeding either alone or in combination with other symptoms compared with 6679 patients with non-rectal bleeding symptoms.[77] The positivity rate of 26.9% at 10 µg/g was lower than the other two studies above but higher than the non-rectal bleeding group at 15.2%. The sensitivity and specificity of FIT in the rectal bleeding group for CRC was 96.6% (95% CI 92.2% to 98.9) and 76.6% (95% CI 75.0% to 78.1%). The PPV was 16.8% (95% CI 15.9% to 17.9%) and NPV 99.8% (95% CI 99.5% to 99.9%). In the bleeding cohort, there were five CRCs with an fHb <10 ug/g, four of which would have been detected with flexible sigmoidoscopy. The group concluded that the use of flexible sigmoidoscopy in patients with rectal bleeding and an fHb <10 ug/g, would reduce the risk of CRC to 0.03%.

The Booth *et al* meta-analysis[61] informing the guidelines identified three studies (n=3665) that reported specifically on rectal bleeding and used colonoscopy or CTC as a reference standard.[17 77 80] The summary sensitivity at a cut-off of 10 µg/g was 96.6% (95% CI 92.8% to 98.8%) and specificity 71.7% (95% CI 70.2% to 73.2).

Iron deficiency anaemia

The Nottingham study, which used a postal FIT in both high and low risk groups described above as per NICE NG12 and DG30 (but excluding rectal bleeding), reported higher fHb levels in those with IDA at 4.8 (0.8–34.1) ug/g compared with 1.2 (0–6.4) ug/g in those without IDA. In this study 40 patients with CRC were identified and using a cut-off of 10 ug/g of fHb, CRC detection rate was 7.2 in those with IDA. In fact, the authors concluded that CRC detection was higher in those with IDA.[74]

Cunin *et al* reported in their cohort of patients where FIT was used in primary care applying the NICE NG12 criteria that 7/48 patients (14.6%) had CRC below the cut-off of 10 ug/g, that is, fHb below threshold cancers.[81] Of the seven fHb below threshold cancers, five had anaemia as well as change in bowel habits and of these, four had true IDA. It was also observed that these six CRCs were right-sided (caecal). The FIT sensitivity for CRC was 80.0% (95% CI 55.7% to 93.3%) in patients with IDA compared with 89.0% (95% CI 70.0% to 97.1%) in those with a combination of other symptoms.

Earlier studies did not report influence of IDA on diagnostic accuracy of FIT.[82 83] More recent data in abstract form applying a definition of IDA of ferritin under 15, reported sensitivity of

Table 4 FIT diagnostic accuracy for CRC at a cut-off of 10 µg/g in patients with high-risk symptoms in the largest and most relevant studies

	Region	Design	Symptoms	n	Analyser	Reference standard	CRC sensitivity @ 10 µg/g	CRC specificity @ 10 µg/g	CRC PPV @ 10 µg/g	CRC NPV @ 10 µg/g
NICE FIT 2021[28]	UK (England)	DTA	NG12	7194	HM-JACKarc	Colonoscopy	92.2% (88.2% to 95.2%)	82.3% (81.2% to 83.2%)	16.2% (14.3% to 18.2%)	99.7% (99.5% to 99.8%)
Turvill *et al*[29]	UK (England)	DTA	All	5040	HM-JACKarc	Various	87.4% (81.0% to 92.3%)	80.9% (79.7% to 81.9%)	12.4% (10.4% to 14.5%)	99.5% (99.3% to 99.7%)
qFIT 2021[62]	UK (England)	DTA	NG12	3596	OC-Sensor	Various	83.3% (75.6% to 91.0%)	80.1% (78.9% to 81.4%)	9.7% (7.6% to 11.8%)	99.5% (99.1% to 99.7%)
McSorley *et al*[31]	UK (Scotland)	SE	All	4841	HM-JACKarc	Colonoscopy	94.7% (91% to 97%)	47% (46% to 48%)	9.4% (8.4% to 10.6%)	99.4% (98.9% to 99.6%)
Mowat *et al*[18]	UK (Scotland)	SE	All	5381	HM-JACKarc	Various	86.7% (78.6% to 92.5%)	79.4% (78.3% to 80.5%)	7.7% (7.1% to 8.4%)	99.7% (99.5% to 99.8%)
Pin Vieito *et al*[21]	Spain	SE	All	5623	OC-Sensor	Various	81.3% (71.3% to 88.3%)	84.1% (83.1% to 85.1%)	6.9% (5.4% to 8.7%)	99.7% (99.5% to 99.8%)
Chapman *et al*[75]	UK (England)	DTA	NG12	732	OC-Sensor	Colonoscopy	89% (75% to 97%)	74% (70% to 77%)	16% (11% to 21%)	99% (98% to 100%)
					HM-JACKarc		84% (69% to 94%)	78% (75% to 81%)	18% (12% to 24%)	99% (98% to 100%)
Farrugia *et al*[73]	UK (England)	DTA	NG12	519	HM-JACKarc	Colonoscopy / CTC	84.9% (68.1% to 94.9%)	81.3% (77.5% to 84.65%)	23.6% (19.6% to 28%)	98.8% (97.2% to 99.4%)
D'Souza 2020	UK (England)	DTA	NG12	160	HM-JACKarc	Colonoscopy	87.5% (52.9% to 97.8%)	84.2% (77.6% to 89.2%)	22.6% (11.4% to 39.8%)	99.2% (95.7% to 99.9%)
Khan *et al*[78]	UK (England)	DTA	NG12	928	HM-JACKarc	Various	85.1% (71% to 93.3%)	83.5% (80.8% to 85.8%)	22.6% (16% to 28.3%)	99% (97.9% to 99.5%)
Nicholson *et al*[27]	UK (England)	SE	All	9896	HM-JACKarc	Record linkage	90.5% (84.9% to 96.1%)	91.3% (90.8% to 91.9%)	10.1% (8.15% to 12.0%)	99.9% (99.8% to 100.0%)
Herrero *et al*[36]	Spain	SE	All	1572	OC-Sensor	Colonoscopy	93.5% (89.1% to 96.3%)	63.4% (60.7% to 66.0%)	28.9% (25.6% to 32.4%)	98.4% (97.2% to 99.1%)
Widlak *et al*[82]	UK (England)	DTA	All	562	HM-JACKarc	Colonoscopy / CTC	80.0% (66% to 93%)	93% (91% to 95%)	44.0% (32% to 56%)	99.0% (98% to 100%)
Arraez *et al*[76]	Spain	DTA	IDA	245	OC-Sensor	Colonoscopy	92.9% (76.5% to 99.1%)	57.1% (50.3% to 63.8%)	21.8% (15.4% to 30.1%)	98.4% (96.2% to 100%)
Khasawneh *et al*[14]	UK (England)	DTA	CIBH	5818	OC-Sensor	CTC	88.9% (79.6% to 94.3%)	80.8% (79.7% to 81.8%)	5.5% (4.3% to 6.9%)	99.8% (99.7% to 99.9%)

95% CIs given in brackets when reported.
CIBH, change in bowel habit; CRC, colorectal cancer; DTA, diagnostic test accuracy study; FIT, faecal immunochemical testing; IDA, iron deficiency anaemia; NPV, negative predictive value; PPV, positive predictive value; SE, service evaluation; SR, systematic review and meta-analysis.

92.0% (95% CI 84.4% to 95.9%) and specificity of 63.2% (95% CI 59.1% to 67.4%)[84] The prevalence of CRC in this cohort with IDA, as expected increased with bands of fHb levels; 1.2% in those with fHb under 9 ug/g, 13.5% in the band 10–200 ug/g and 38.9% in those with cut-offs >200 ug/g. Another study in abstract form, suggested that fHb offered similar discriminatory values to symptoms and even younger patients.[85]

Previous BSG guidelines do not recommend use of FIT in those with IDA.[86] Reasons for their recommendation (evidence strength low; statement strength weak) was related to publication bias in that iron deficiency anaemia may be over-represented in those with fHb below a threshold of 10 ug/g CRCs. However, the larger and subsequently published NICE FIT and qFIT studies more recently have provided further consistent data which supports the use of FIT testing in people with IDA.[28 62]

The meta-analysis informing the guidelines identified two studies (n=724) that reported specifically on IDA and used colonoscopy or CTC as a reference standard.[72 76] The summary sensitivity at a 10 µg/g cut-off was 96.7% (95% CI 88.7% to 99.6%) and specificity 73.6% (95% CI 70.1% to 76.9%).[61]

Change in bowel habit

Few studies have specifically reported on accuracy of FIT for CRC in patients with change in bowel habit (CIBH). Further, the definitions used make it more difficult to collate these together to form a unified consensus. In the Nottingham primary care study CIBH had lower CRC detection rates 4.5% versus 7.4% compared with those with IDA at a cut-off of 10 ug/g.[74] The NICE FIT study suggested that the sensitivity of FIT for CRC at a cut-off of 10 ug/g in patients with CIBH, was higher in the older population (over 60 years of age) compared with those under 60 years of age (85.9% vs 60%), respectively.[72]

The large 38 765 participants in the Spanish primary care study,[21] reported broadly similar findings even when applying cut-offs of 10 or 20 ug/g/faeces.[78] In fact, the number needed to scope for those presenting with diarrhoea was 15 and constipation 16.2 at 10 ug/g compared with 12.8 with diarrhoea and 13 with constipation at 20 ug/g.

The meta-analysis informing the guidelines identified two studies (n=10 067) reporting specifically on CIBH symptom and used colonoscopy or CTC as a reference standard. The summary sensitivity and specificity at 10 µg/g were 85.6% (95% CI 79.0% to 90.8%) and 83.6% (95% CI 82.9% to 84.3%), respectively.[61]

Evidence summary

1. FIT is highly sensitive for CRC in symptomatic patients with most large studies reporting a sensitivity of >87% at the commonly used cut-off of 10 µg/g.
2. The diagnostic accuracy of FIT is similar in both high and low risk symptomatic patients, irrespective of the cut-off used.
3. FIT is not always detectable in patients with rectal bleeding and is a useful evaluation tool when CRC is suspected. FIT is highly sensitive for CRC in patients with rectal bleeding with a sensitivity of >90% at a cut-off of 10 ug/g. Patients with negative FIT and persistent rectal bleeding can be safely investigated with flexible sigmoidoscopy and appropriate safety measures in place.
4. The evidence for use of FIT for the detection of CRC in IDA supports its use at a cut-off of 10 µg/g. If a lower cut-off is applied, then the accuracy further improves.
5. The evidence for use of FIT for the detection of CRC in those with isolated change in bowel habit is less clear although UK data suggests greater benefit in those over 60 years (while the Spanish data are consistent with other symptoms).

DIAGNOSTIC ACCURACY AND PATIENT-RELATED FACTORS

There is currently insufficient evidence to recommend variations in the fHb threshold for referral from primary care according to patient related-factors.

GRADE of evidence: low; Strength of recommendation: Strong.

In summary, age and gender may affect FIT performance but findings are inconsistent. There is no evidence to suggest that these are significant enough to warrant variations in thresholds at present—very young patients without genetic predisposition in whom the risk of CRC is very low may be the exception, however there is no evidence to exclude such individuals from FIT testing pathways currently. Therefore, in the absence of specific evidence to the contrary, the same fHb threshold should be used irrespective of patient-related factors (including: age-group, gender, ethnicity, deprivation and concurrent medication).

FIT, demographics and colorectal cancer

Demographic variations in CRC incidence are well recognised[87] as are variations in fHb from screening studies.[88 89] CRC diagnoses rise with increasing age and it is known that fHb also rises with age, even in the absence of notable pathology. CRC incidence is higher in men overall but also in the male population referred by GPs for further investigation. Deprivation has been noted to be a risk factor for men rather than women.[88] A number of studies on FIT in symptomatic patients report higher fHb in men than in women, although Bailey *et al*'s study[11] in a restricted DG30 population notes high fHb levels in women aged 30–40 years specifically. Men with CRC show a predilection to the rectum and one group has suggested false negatives in palpable rectal mass where a bleeding tumour would present overtly; CRCs in women are associated with the right colon and most studies report lower fHb in this group of cancers, most likely due to distribution of blood throughout a formed stool reducing concentration and increasing risk of sampling error. Although many studies show some differences in fHb by age and gender, findings are inconsistent, and this is perhaps unsurprising given the complexity of the potential interactions described and the size of cohort needed to address all of these. Furthermore, FIT is a test for occult blood in stool which may be related to many other pathologies with different interactions with demographics, or no identifiable pathology at all, adding further complexity to this challenge.

Age

A number of papers have reported data relevant to diagnostic performance of FIT by age. Interpretation is complicated by the different age categorisations, FIT thresholds and outcomes considered, as well as variations in the study populations and endpoints. Moreover, not all of the studies reported on diagnostic performance in terms of sensitivity, specificity and/or area under the curve (AUC).

A subanalysis of the NICE FIT study[28] assessed diagnostic accuracy in 1103 patients under 50 years of age preselected by GPs for urgent referral to secondary care.[90] All patients were well enough to undergo colonoscopy, thus potentially excluding some older and frailer patients. At all FIT thresholds, sensitivity for the older group exceeded that for the younger age group. At a threshold of 10 µg Hb/g faeces sensitivity was 87.5% for those <50 years of age versus 97.4% in those ≥50 years of age.

At the 2 µg Hb/g faeces threshold, specificity was higher for the younger group (70.4% vs 64.1%); at the 10 µg Hb/g faeces threshold, specificity was almost identical in the two groups (83.6% vs 83.5%); and at the 150 µg Hb/g faeces threshold, it was slightly higher in the older group (92.2% vs 94.9%). At all thresholds, the PPV for the older groups was more than double that for the younger group (PPV was 6.8% vs 17.1% in those over 50y at 10 µg Hb/g faeces). Despite these differences, further analysis of the 329 CRCs which were detected in this selected population found there was no association between age and FIT status (negative/positive) at a threshold of 2 or 10 µg Hb/g faeces. The CRC prevalence in the younger age group was 1.5% and the study was not powered to assess younger patients specifically. Furthermore, the authors point out the value of detecting inflammatory bowel disease (IBD) and other pathology in younger patients.

The Fast Track FIT study[29] of 5040 patients preselected by GPs for urgent referral, all completing either colonoscopy, CT colonography or CT abdomen and pelvis, compared groups above and below 60 years of age. AUC was slightly lower for those aged 60+ years of age (0.88, 0.85–0.92) compared with 1217 younger patients (0.92, 0.88–0.96), but the 95% CIs for these estimates overlapped. In this cohort, sensitivity and specificity were slightly higher in the younger group (sensitivity: 90.0 vs 83.5; specificity: 87.4 vs 85.4); PPV and NPV did not differ. The authors describe an optimal cut-off threshold of 37 µg Hb/g faeces for those under 60 years of age, compared with a baseline of 20 µg Hb/g faeces for those over 60 years of age. In an earlier study[53] this group also reported on 515 individuals similarly selected for investigation, in whom the FIT threshold to achieve optimal AUC for CRC detection again needed to be higher for younger patients (<65 years of age: FIT threshold ≥46 µg Hb/g faeces for AUC of 0.89 (0.722–1.000); 65+ years of age threshold ≥12 µg Hb/g faeces for AUC of 0.91 (0.842–0.981). However, these findings were based on only 7 cancers in the younger age group and 19 in the older group.

A small study of 404 patients,[91] referred to secondary care for colonoscopy, in whom overall sensitivity and specificity of FIT at a threshold of 20 µg Hb/g faeces for CRC were 87.5% and 83.7%, respectively. FIT performance for relevant colonic pathology showed sensitivity of 50.6% and specificity of 69.6%; sensitivity was slightly lower and specificity slightly higher in those aged under 50, compared with those aged 50 and older. This study used a different FIT platform to most published studies (FOB Gold).

The largest study commenting on age reported on FIT in primary care use in Northern Spain and included 38 675 patients (CRC prevalence 1.7%) with a variety of symptoms.[21] This study used 2 years registry-based follow-up as an endpoint and therefore the majority are not investigated in secondary care. However, the group reported diagnostic accuracy data based on follow-up and found no significant differences in sensitivity across three age strata: <50 years of age (93.1% at 10 µg Hb/g faeces; 91.8% at 20 µg Hb/g faeces), 50–69 years of age (91.5% at 10 µg Hb/g faeces; 88.7% at 20 µg Hb/g faeces) and >69 years of age (89.8% at 10 µg Hb/g faeces; 87.2% at 20 µg Hb/g faeces) although the values declined with increasing age at both cut-offs. They reported differences in specificity which fell significantly with rising age at a threshold of 10 µg Hb/g faeces (88.5% <50 years of age, 83.6% 50–69 years of age and 75% >69 years of age). In this study, the prevalence in the population under 50 years of age was only 0.3% and raising the threshold to 20 µg Hb/g faeces had the least detrimental effect on missed cancers in this age group; although the overall increase in missed CRC across the whole population at 20 µg Hb/g faeces was <1 in 1000.

Gender

Two large studies of FIT in high-risk cohorts selected for and completing secondary care investigation have reported diagnostic accuracy by gender. The NICE FIT study[28] found no association between sex and FIT status using a cut-off of either ≥2 or ≥10 µg Hb/g faeces to define positivity. By contrast, the Fast Track FIT study[29] found that, to achieve the optimum AUC for CRC, different FIT cut-offs would be needed for men and women; 21 µg Hb/g faeces for men and 16 µg Hb/g faeces for women gave AUC of 0.89 and 0.88, respectively. In their earlier, smaller, study of 515 patients, Turvill *et al*[53] reported that the optimal FIT cut-off for detecting CRC was ≥22 µg Hb/g faeces for men (AUC=0.909, 0.835–0.983) and ≥12 µg Hb/g faeces for women (AUC 0.891, 0.744–1.000); but these results were based on 18 cases of CRC in men and 8 cases in women. In a study of 928 patients[78] (41% men), FIT at a threshold of 10 µg Hb/g faeces had lower sensitivity for the detection of bowel disease (CRC, high-risk polyps or colitis) in women than in men. Sensitivity was 95.4% (95% CI 75.1% to 99.7%) for men compared with 76.1% (95% CI 54.5% to 89.9%) for women. Specificity was slightly higher in women (men: 80.5% (95% CI 75.9% to 84.4%); women: 85.5% (95% CI 82.2% to 88.4%).

In their large primary care study (n=38 675) with follow-up, rather than full investigation, Pin Vieito *et al*[21] also reported higher sensitivity (91.6% vs 88.4%) but significantly lower specificity (79.9% vs 82.6%) in men at 10 µg Hb/g faeces. In a similar UK study of 9896 patients (41% men), where not all patients were investigated, Nicholson *et al*[27] reported that the AUC for both CRC was almost identical in men (0.933) and women (0.948).

Age and gender

Nicholson *et al*[27] also reported the AUC for FIT at a threshold of ≥10 µg Hb/g faeces for the detection of CRC if testing was restricted to different age groups. Restricting testing to people aged 80+ was the only instance where the AUC dropped below 0.90. If FIT testing, was to be restricted to those aged 40+, the AUC would be 0.944 (95% CI 0.899 to 0.988) for women and 0.934 (95% CI 0.897 to 0.972) for men; if limited to the 60+ age group, the AUC would be 0.919 (95% CI 0.856 to 0.982) for women and 0.921 (95% CI 0.870 to 0.971) for men; and if limited to those aged 70 and older, it would be 0.934 (95% CI 0.867 to 1.000) for women and 0.936 (95% CI 0.895 to 0.978) for men. In women, the AUC would be highest (0.708) when testing was to be restricted to those aged 50 and older; in men it would be highest if testing was restricted to those aged 70+.

Multivariate analyses including age and gender

A number of groups have reported multivariate analyses including demographics (with symptoms, blood results and other factors) as covariates and fHb measured by FIT is consistently the most predictive factor by some margin.[14 25 92–95] No other factor reaches significance consistently, although increasing age and male gender appear most frequently.

The FAST score, combining age and gender with FIT, was developed in Northern Spain in patients undergoing colonoscopy,[92] but has failed to show improved clinical effectiveness compared with FIT alone when trialled in a broader population in Tayside[96] and when applied to the NICE FIT data set.[28] It is not clear whether the use of different platforms affected these findings, as well as other intrinsic

differences in the cohorts evaluated. The ColonFlag score[52] takes this approach a step further, combining FBC results with fHb, age and sex, and showed improved specificity compared with FIT—taking an AND/OR approach sensitivity improved to 100%. However, this study is relatively small and needs further validation. A similar sized study (n=408) by Digby *et al*[34] found no value in other factors, including demographics, other than family history.

A much larger study by Withrow *et al*[93] reported on 16 604 patients tested in primary care (and includes the cohort from Nicholson *et al*)[27] specifically focussing on the value of combining FIT with blood tests. However, the majority of patients were not investigated. In a variety of models, they found no value in including age. They also reject the value of models including gender, although they note that the threshold to reach a 3% PPV is slightly higher in men (25 µg Hb/g faeces) than in women (17 µg Hb/g faeces). Consistent with this, Rodriguez-Alonso *et al*[94] found that, after accounting for FIT, sex was statistically significantly associated with both CRC and advanced neoplasia and men had more than twofold increased risk of disease. They found age did not need to be included in a multivariable model for CRC, after FIT (and gender and IDA) had been included. However, when an outcome of advanced neoplasia was considered in a model including FIT result and gender, risk increased with increasing age.

There is insufficient evidence that diagnostic performance of FIT for the detection of colorectal neoplasia varies by ethnicity, deprivation and other factors.

Ethnicity and deprivation

Although some studies provide breakdown of populations by ethnicity and deprivation, none have looked at this as a primary outcome and there is no clear data on variations in diagnostic accuracy. Even in larger data sets the low event rate in non-white categories or specific deprivation groups appears too small and there are no pooled analyses that address this. The NICE FIT study[28] compared the characteristics of 329 patients detected with CRC, all of who had undergone an FIT, were compared according to notional FIT status. At a positivity threshold of either ≥2 ug or ≥10 Hb/g of faeces, there was no statistically significant difference in the ethnic distribution of those who would have been classified FIT positive or FIT negative. The same observation was made for deprivation category of area of residence. A questionnaire based evaluation of the NICE FIT cohort suggests lower acceptability in non-white ethnic groups.[40] The group in Nottingham have also reported some evidence that the non-return of FIT kits is associated with younger age, male sex, non-white ethnicity and higher deprivation populations (Abstract added to library). These findings mirror studies in screening and have implications for education, implementation and safety netting, rather than diagnostic accuracy per se.

Other factors

As noted earlier, Digby *et al*[34] reported on family history and after adjusting for FIT result (and rectal bleeding and folate level) a family history of polyps was associated with a more than eightfold increased risk of any significant bowel disease (CRC, advanced adenoma (AA) or IBD) (OR=8.21, 95% CI 1.74 to 38.78). Only nine people with a family history of polyps had significant bowel disease.

A single study[60] has examined associations between smoking and body mass index and risk of advanced colorectal neoplasia, once FIT had been taken into account. There was a significant association between being a current or ex-smoker and risk of advanced colorectal neoplasia (ACN) (multivariate OR=1.51, 95% CI 1.02 to 2.29). Body mass index greater than 25 kg/m^2 was not significantly associated with ACN.

Evidence is too limited to conclude whether the diagnostic performance of FIT varies in people using specific medications.

Medications

In total five publications have reported on diagnostic accuracy of FIT in patients using particular medications. Two studies examined proton pump inhibitor (PPI) use. Rodriguez-Alonso *et al*[97] included 1002 patients referred for colonoscopy; 40% were PPI users. In total 133 patients had advanced neoplasia (AN) and 30 patients had CRC. There were no differences in sensitivity or specificity of FIT with a positivity threshold of ≥20 ug Hb/g of faeces for the detection of CRC among those who used PPIs and those who did not. When AN was considered, both sensitivity and specificity were significantly lower for PPI users (sensitivity: 43.0%; specificity: 86.9%) than non-users (sensitivity: 65.6%, p=0.009; specificity: 92.3%, p=0.010). The second, smaller, study of 612 patients[98] published only as an abstract, reported that sensitivity of FIT at a threshold of 10 ug/g for advanced neoplasia (n=55) was lower in PPI users than non-users (54% vs 81%, p=0.05), while specificity did not differ. The area under the receiver operating characteristic curve was 74% (95% CI 0.58 to 0.91) for PPI users compared with 0.92 (95% CI 0.89 to 0.95) for non-users.

Three publications considered the possible influence of use of antiplatelet or anticoagulant medication on FIT diagnostic accuracy. Two reported on data from the COLONPREDICT study; the first, an abstract from 2014, included 1567 patients;[92] the second, a full paper published in 2018, included 3052 patients.[99] The smaller study reported that the diagnostic accuracy of FIT for CRC was significantly lower among those taking antiplatelet and/or anticoagulant medication (AUC: users 0.81; non-users, 0.88; p=0.04). The larger study focused on aspirin specifically in a study in which 16% of patients used aspirin. Continuous treatment with aspirin did not influence sensitivity, specificity of the AUC of FIT for either CRC detection or AN detection at a threshold for positivity of ≥20 ug of Hb/g of faeces. In a subgroup analysis of patients using ≥300 mg/day aspirin, sensitivity, specificity and AUC were lower, as was polyp prevalence, than among aspirin non-users, but this group included only 58 people and the differences were not statistically significant. The final study reported only multivariable modelling results[99] and use of anti-coagulants, anti-platelets or non-steroidal anti-inflammatory drugs (NSAIDs) was not significantly associated with advanced colorectal neoplasia after adjusting for FIT results.

There is currently insufficient evidence to confirm whether diagnostic accuracy is impacted by the type of FIT analyser used.

GRADE of evidence: low; Strength of recommendation: weak

There is no international standardisation of FIT methods meaning that different results could be obtained on different manufacturer systems.[100] Despite this, in symptomatic testing, single thresholds for referral have been recommended.[5]

To date there are only two peer-reviewed publications that have directly compared results obtained on two different FIT analytical systems when patients have taken samples from the same bowel motion in a symptomatic pathway.[75 101]

In the first study[75] 732 patients returned both an OC-Sensor and an HM-JACKarc collection device. They had been instructed to collect samples into each device from the same bowel motion. Correlation of results was carried out and agreement at cut-offs of 4, 10 and 150 µg Hb/g faeces (µg/g) were assessed. To act as a

control 114 patients collected two samples using two OC-Sensor devices. At thresholds of 4, 10 and 150 µg/g the Cohen's kappa have concluded that there is not enough data to comment on the comparative performance is 0.74, 0.79 and 0.76, respectively, which is interpreted as substantial agreement. When two OC-Sensor devices are compared the Cohen's kappa are 0.80 (substantial agreement), 0.91 (almost perfect agreement) and 1.00 (almost perfect agreement) respectively. This suggests that the referral rate will vary dependent on which of the two methods is used.

In terms of diagnostic accuracy, at thresholds of 4, 10 and 150 µg/g, OC-sensor had a higher sensitivity and lower specificity than HM-JACKarc for CRC. Thus, based on this study, employing the same thresholds for the two methods OC-Sensor will generate more referrals however it will also detect more CRCs than HM-JACKarc at the same thresholds.

In the second study[101] the QuikRead Go (QRG), a quantitative point of care FIT test which had previously undergone independent analytical evaluation[102] was compared with the FOB Gold wide method on the SENTiFIT laboratory analyser. Five hundred and fifty-three patients provided paired samples for both methods and underwent colonic investigations that were suitable to give definitive diagnostic outcomes. Fourteen patients were diagnosed with CRC. QRG reported one false negative. FOB Gold reported no false negatives. Thirty per cent of QRG results were >10 ug/g would have resulted in referral compared with 16.9% for FOB Gold wide.

In an unpublished study,[103] 233 patient returned FIT devices from four different FIT systems collected from a single bowel motion. To act as a control a further 189 patients returned two FIT devices from the same FIT system. Differences were observed in the referral rates for different methods and the categorisation according to Cohen's kappa, specifically for one method more than the other three. There were only seven CRCs detected in the four FIT group so inadequate data to comment conclusively on the comparative diagnostic accuracy of the different FIT tests.

In addition to the three studies above, four systematic reviews have commented on the different FIT assays available.[7 26 65 66] The conclusions were that there are a lack of studies directly comparing the performance of different FIT assays and that there are currently no data on the comparative performance of different FIT assays. In addition, it was reported that the limited number of studies, the majority of which were using OC-Sensor, along with high study heterogeneity, did not enable conclusions to be drawn from combining data from different studies.

FIT COMBINED WITH OTHER FACTORS TO OPTIMISE RISK STRATIFICATION

There is currently insufficient evidence to recommend including FIT in a risk score with other clinical features to identify patients with symptoms of suspected CRC.

GRADE of evidence: low; Strength of recommendation: weak.

There is some supporting and emerging evidence that combining fHb with either a composite score or another biomarker, improves CRC detection. However, these methods have not yet been clinically validated.

Several scoring systems have been reported either in combination with fHb or in comparison with fHb alone to improve detection of CRC. The FAST score devised initially by the Spanish group uses a combination of age, sex, fHb at different cut-offs.[104] As expected, when using a lower FAST score cut-off (>2.12) provided almost 100% sensitivity with poor specificity 14% and a 100% NPV.[104] For detection of advanced neoplasia in a British population, there was a 10% improvement compared with fHb on its own.[105] By contrast, Digby *et al*[96] did not show any benefit of using the FAST score compared with fHb on its own. The latter was in a primary care setting where a quarter had a colonoscopy for final diagnosis.

FAST score also performed less well against ColonFlag (an Israeli trademarked algorithm) that comprises FBC, red cell indices, ferritin, iron and transferrin. CRC accuracy was reported to provide sensitivity of 100% compared with 73% with FAST score. Specificity was poor at 50% with ColonFlag but 81% with FAST score and NPVs of 99% and 100% for FAST score and ColonFlag, respectively.[52] Using a lower of two proposed cut-offs for ColonFlag, CRC accuracy resulted in a sensitivity of 80%, specificity of 48% and NPV of 99% (sample size was limited to 21 cases).[106]

ColonPredict[107] which used a combination of symptoms, fHb, serum haemoglobin and mean cell volume was deemed superior to symptoms alone while ColonoFIT,[60] which uses three serial fHb measurements in a week, patient questionnaire, medication consumption (eg, NSAIDs) had a ninefold higher OR of detecting CRC than serial fHb on its own. The RAT (research assessment tool) which comprises clinical, demographic, fHb, blood markers and colonoscopy outcome seems to hold promise with diagnosis of bowel disease (defined by authors as CRC and significant adenoma but excluding IBD). The OR was 9 (4.3–18.6) using the RAT tool compared with 5.3 (2.4–11.7) with fHb on its own (Lord *et al*, 2018). The Health Technology Assessment from 2017,[63] using 10 studies (including 9 from secondary care), demonstrated that fHb on its own was still more effective and cost-effective compared with faecal occult blood testing or using no triage test.

Volatile organic compounds (biomarkers of cellular inflammation and/or cancer)[108] have shown some promise with Widlak *et al*[82] showing improved CRC detection in those who are tested negative with fHb (<10 ug/g faeces) in terms of improving its sensitivity from 80% to 97%. A recent network meta-analysis of both fHb and volatile organic compounds for CRC detection demonstrated the probability of CRC detection improving from 0.5% to 0.1% when both tests were negative.[108]

FIT IN SPECIFIC POPULATIONS

We suggest that FIT may be used to stratify adult patients aged younger than 50 years with bowel symptoms suspicious of a diagnosis of CRC.

GRADE of evidence: low; Strength of recommendation: weak.

The incidence of CRC in younger patients under the age of 50, also known as early onset CRC, has been documented in studies across developed healthcare economies.[109–115] Recent studies suggest incidence in this age group is rising. We suggest that FIT may be used to stratify adult patients aged younger than 50 years with bowel symptoms suspicious of a diagnosis of CRC referred from primary care for further investigation, at the same threshold as for older patients. CRC incidence will be low in younger patients at 'low' FIT thresholds, but FIT would be of value to detect other serious bowel disease in this group.

CRC can be difficult to detect on the basis of symptoms in younger patients, as these may frequently overlap with common benign conditions. For example, change in bowel habit or abdominal pain may be due to irritable bowel syndrome, and rectal bleeding is frequently caused by haemorrhoids in younger patients. A diagnostic test that can identify those younger patients at risk of cancer may therefore be useful as an adjunct to decide on referral to secondary care for further investigation.

The diagnostic accuracy data of FIT in younger patients (<50) was the primary endpoint in one study,[116] but reported in subgroup analyses in three further studies.[13 29 53] Souza *et al* investigated the diagnostic accuracy of FIT in 9822 symptomatic patients in the UK, and had a particular focus on 1103 symptomatic patients under the age of 50.[116] The prevalence of CRC was 1.5% (16/1103) in younger symptomatic patients. The sensitivity of FIT for younger patients aged <50 was 87.5% (95% CI 61.7% to 98.4%), 81.3% (95% CI 54.4% to 96.0%) and 68.8% (95% CI 41.3% to 89.0%) at fHb cut-offs of 2, 10 and 150 µg/g, respectively; specificity at these cut-offs was 70.4% (95% CI 67.6% to 73.1%), 83.6% (95% CI 81.3% to 85.5%) and 92.2% (95% CI 90.4% to 93.7%). At each threshold, the sensitivity was lower for younger patients than for patients aged 50 and older, but specificity was higher, and the differential between age-groups narrowed as the threshold rose. In those under 50 years of age, the PPV for CRC increased from 4.2% (95% CI 2.3% to 6.9%) to 11.5% (95% CI 5.9% to 19.6%) at cut-offs of 2 and 150 µg/g. The higher prevalence of IBD in younger patients meant that the PPV of FIT for serious bowel disease (CRC, IBD and AA) was high, increasing from 31.3% (95% CI 26.3% to 36.5%) to 65.6% (95% CI 55.2% to 75.0%) at the same cut-offs.

In a study in Denmark, of FIT in patients over the age of 30 with low-risk symptoms the prevalence of CRC was low at 0.5% (4/848) in the subgroup of patients under the age of 50 and no cancers were detected in those aged under 40.[13] The PPV of FIT (>10 µg/g) for CRC in the 40–49 age-group was only 0.6% (0.1%–1.3%). In a study from Spain, Lue *et al* reported diagnostic performance of FIT at a threshold of 20 µg/g for the detection of any relevant colonic pathology (CRC, AA, IBD, microscopic colitis or angiodysplasia). In the subgroup aged under 50 (n=119), specificity and NPV exceeded 90% (specificity: 92%; NPV 90.2%) but sensitivity was only 47.4% and PPV was 52.9%.[91] Finally, in a mixed population of 38 675 asymptomatic and symptomatic patients (8866 aged <50), not all of whom underwent colonoscopy or other diagnostic investigation, Pin Vieito *et al*[21] found that sensitivity and specificity of FIT at a threshold of 10 µg/g for the detection of CRC up to 2 years later in those aged under 50 were 93.1% (95% CI 78.0% to 98.1%) and 88.5% (95% CI 87.9% to 89.2%), respectively. PPV in this younger age-group was 2.6% (1.8%–3.8%). The authors reported that sensitivity did not vary by age, but that specificity was lower, and PPV was higher, in older patients (50–69 and 70+) than in those under 50. The finding that right-sided CRC are more likely to be missed by FIT suggests that younger patients, who are more likely to present with distal left-sided CRC, may not be at increased risk of false negative FIT.

In summary, FIT can be used to risk stratify the risk of CRC or serious bowel disease in younger patients (aged <50). The prevalence of CRC in symptomatic patients and the sensitivity and PPV of a positive FIT, is lower in younger than older patients. However, other serious bowel conditions may cause a positive FIT and merit investigation, particularly when higher fHb concentrations are detected. Further research is needed to confirm the diagnostic accuracy of FIT specifically in younger patients, the optimal FIT threshold and whether testing should be limited to those older than a specified age (eg, 40 years); the relative costs and benefits (in terms of detection of both CRC and other colonic pathology) of different strategies are not clearly established.

INVESTIGATION IN SECONDARY CARE

Colonoscopy is considered the standard method of investigation, however other methods of colorectal imaging may be appropriate in some patients

GRADE of evidence: low; Strength of recommendation: weak.

We recommend that for patients with symptoms of a suspected diagnosis of CRC, CTC is equivalent to colonoscopy for detection of CRC (the choice of modality should be determined by the local expertise and availability).

GRADE of evidence: low; Strength of recommendation: Strong

There is currently insufficient evidence to support use of a specific quantitative FIT threshold to recommend the selection of CTC versus colonoscopy

GRADE of evidence: very low; Strength of recommendation: weak.

In this section we considered the evidence for colorectal investigation in patients with signs or symptoms of a suspected diagnosis of CRC, however there is limited available direct evidence in this specific population with an FIT above threshold with most studies reporting colonoscopic outcomes as a reference standard. In the UK NHS, only colonoscopy and CTC are established appropriate whole colon investigations for the exclusion of CRC and large polyps in patients with symptoms suggestive of CRC. CTC has superseded barium enema examinations. Colonoscopy in the UK is quality assured by the Joint Advisory Group for GI endoscopy, which has led to steady improvements in service quality,[117] enables biopsies to be taken at index investigation and more effective diagnosis of non-neoplastic pathology.

Historically colonoscopy was the criterion standard for lower GI investigation allowing both direct visualisation and biopsy or polypectomy in a single procedure; however from 2005, NICE guidance supports the use of CTC as an alternative test to colonoscopy with adequate evidence on safety and efficacy.[30] Guidance from European Society of Gastrointestinal Endoscopy/European Society of Gastrointestinal and Abdominal Radiology (ESGE/ESGAR) in 2020 recommend CTC as an acceptable and equally sensitive alternative for patients with symptoms suggestive of CRC when colonoscopy is contraindicated or not possible (strong recommendation, high quality evidence). Because of lack of direct evidence, ESGE/ESGAR did not recommend use of colon capsule endoscopy (CCE) in this situation (very low quality evidence[118]). CTC is safe with complications rarely encountered and rarely serious.[119 120] CTC is well tolerated even when colonoscopy is contraindicated or incomplete and frequently used in older patients.

The SIGGAR study,[121] a landmark multicentre randomised study of 1610 patients with symptoms suggestive of CRC from 21 UK NHS hospitals showed:

1. Detection rates for large polyps or CRC colonoscopy and CTC were the same at 11%.
2. Referral rates for additional colonic investigation was 30% for CTC and 8% for colonoscopy.
3. 10% of patients had a significant extracolonic finding at CTC: 2% had extracolonic malignancy and 3.5% had an extracolonic diagnosis that at least part explained presenting symptoms.
4. Incompletion rate for CTC was 4% versus 7% for colonoscopy.

The SIGGAR study also showed that the patient acceptability and psychological impact of investigation via CTC or colonoscopy was similar.[122]

A systematic review and meta-analysis by Obaro *et al*[4] of interval cancer rates (post imaging CRC rates) for CTC and colonoscopy have been published recently. A systematic review and meta-analysis by Obaro *et al*[123] showed a post CTC CRC rate of 4% (4.4 missed cancers per 100 detected, with low heterogeneity) which is within the range reported for colonoscopy (3%–9%).[124] Systematic review and meta-analysis of CTC after positive faecal occult blood test or FIT showed CTC had high per-patient sensitivity (89%) for 6 mm+ lesions (adenomas or cancer) and pooled sensitivity for cancer of 96% (low heterogeneity). Specificity for polyps (6 mm+) was lower (75%) and heterogeneous with performance contingent on centre.[125]

CTC has a potential advantage over other whole colon investigations by also detecting of extracolonic malignancy or other life-threatening conditions such as symptomatic abdominal aortic aneurysm which may be responsible for symptoms. A 2WW pathway audit of 1792 straight to CTC patients identified non-colonic cancer in 4.3% patients and 12% had a new, potentially significant extracolonic finding.[126] A 2018 systematic review and meta-analysis (44 studies included from screening and symptomatic populations)[127] showed potentially significant extracolonic findings in 5.2% of symptomatic individuals. The rate increased to (5.7%) for those aged over 65 years versus 2.3% for those younger than 65 years with an 8% overall referral rate for additional investigation of these findings.

Concerns about 'over investigation' of false positive or unimportant findings following CTC appear overstated as patients and their referring clinicians are prepared to accept a much higher rate of additional investigations (in up to 100% and 40% of examinations, respectively) than occurs in real-world practice.[128]

There is no evidence for selecting one whole colon examination over another on the basis of FIT level in terms of diagnostic accuracy or enhanced patient pathway. While intuitively beneficial, there is a lack of evidence recommending use of CTC for patients with symptoms of abdominal pain and weight loss. Similarly, there is no specific evidence favouring CTC over colonoscopy or vice versa below a specific FIT threshold, despite a relative increase in the likelihood of extracolonic pathology with lower FIT levels. A 2007 study showed symptomatic patients with no colonic abnormality are more likely to have an important extracolonic finding[129] and extracolonic findings could account for 10% of patients' symptoms at initial presentation.[130]

CTC does not offer immediate biopsy or polyp resection with even the most experienced centres referring approximately 10% of cases to endoscopy, potentially slowing patient pathways, although these levels will be considerably higher in a 'FIT above threshold' population.[3 131]

The small dose of radiation administered with CT colonography can be minimised with newer state-of-the-art CT platforms and protocols (equivalent to approximately 1-3 years of background radiation in the UK), including routine use of dose modulation and ultra-low dose protocols for younger patients. However, as a general rule, radiation associated tests should be used judiciously according to assessment of risk/benefit as governed by IRMER (Ionising Radiation (Medical Exposure) Regulations) with particular caution in younger patients[132].

Currently there is an NHS CCE trial which will provide data on the utility of this intervention in the investigation of this patient population, however to date there is no direct evidence in the symptomatic population.[133] Early indirect evidence from the SCOTCAP study suggest that CCE may be well-tolerated, although that there is a high rate of incomplete examination.[134] There is a suggestion CCE may be considered in some lower risk populations whereby colonoscopy might be avoided. In due course the NHS England trial will provide further relevant data to inform the use of CCE in the near future, however currently there is no published data of the diagnostic accuracy of CCE in people with symptoms of a suspected diagnosis of CRC.

ACCEPTABILITY

On the basis of limited evidence, clinicians and patients consider FIT as an acceptable test for symptomatic CRC in most circumstances

GRADE of evidence: very low; Strength of recommendation: weak

We recommend that services should consider ways of promoting a high proportion of patients to return an FIT kits.

GRADE of evidence: very low; Strength of recommendation: Strong.

In summary, studies which report the uptake in symptomatic populations demonstrate an uptake of between 78.9% and 94%. There was some suggestion that younger age groups found the FIT kits less acceptable to complete which may need to be explored in more detail and addressed. These results suggest that the test has a high degree of acceptability. Patients prefer the non-invasive FIT kits over colonoscopy as long as its accuracy is comparable, however GPs' acceptance prior to COVID-19 was more limited. More resources need to be invested when publishing these new guidelines with audit and evaluation demonstrating that all areas of the country are delivering an equitable service.

In this systematic review observational or qualitative studies were identified including those which reviewed FIT kit response rates and the practice of the referring clinicians. There is little 'direct' evidence of acceptability studies of the use of FIT in symptomatic populations.

Von *et al*[135] surveyed 1057 adults aged between 40 and 59 to imagine they had symptoms of CRC and answer a survey exploring their choice of FIT versus colonoscopy as a diagnostic test. Potential 'miss rates' of CRC were suggested. Interestingly 150 chose neither test, while 70% chose FIT when the miss rate was equivocal in both FIT and colonoscopy but when the miss rate was increased by one person in the FIT group the acceptance reduced to 40.4%. Information of a normal result by letter was preferred by 62.2% of the patients while 32% wanted face-to-face appointment to discuss abnormal result and 7.1% would still chose FIT even with a 10% reduction in accuracy compared with colonoscopy. One-third of GPs preferred to use FIT to 'rule out' colonoscopy but there was confusion over symptoms and optimal use of FIT. The majority of GPs were still not using FIT routinely at the time of the survey.

Digby *et al*[96] report that of 4072 FIT who were sent by secondary care to patients presenting with lower bowel symptoms, 2881 returned their FIT kits, suggesting a return rate of 70.75%.

In a service evaluation of FIT and anaemia for risk stratification in the 2-week pathway for CRC, 1106 FIT kits were sent with a return rate of 80.9%.[74]

Maclean *et al* asked 381 symptomatic patients to undergo FIT[136] with 358 (94%) samples were returned. Onward referral for colonoscopy reduced from 62% to 34%. Follow-up of all the patients over a 2-month period found one person who had returned a positive FIT but had declined investigation because of fears over COVID-19, had later been diagnosed with CRC.

Ng *et al* stated that 17 out of 19 patients (89.5%) referred by the GP on 'non-cancer pathways' and 348 out of 441 referred into the urgent cancer pathway (78.9%) had returned their FIT kits within 7 days and overall 94.4% returned their kits with 14 days.[137]

Chapman reviewed 1862 patients referred to their GP with lower GI symptoms,[32] 91.4% returned their kits within 7 days, however the authors noted that those not returning their FIT kits were significantly younger than those who did.

A recent qualitative survey of symptomatic patients assessed usability and acceptability of FIT and reviewed 1151 patients who had reported symptoms of CRC and sent FIT tests.[40] A relatively high 90.2% found the kits straightforward to use, 76.3% disagreed that the tests were unhygienic and 78.1% preferred FIT to colonoscopy.

In 2018, Von *et al* explored the attitudes of GPs towards FIT in patients at an increased risk of CRC.[138] One-third preferred to use FIT as a 'rule out' test. They were more willing to use FIT if the GPs were aged between 36 and 45, considered FIT to be highly accurate, thought the patient would benefit FIT over immediate colonoscopy, and were highly confident about discussing FIT tests. GPs were also less willing to offer FIT if they referred more than 10 patients onto the 2WW pathway per year or thought the patient needed a longer consultation for FIT. This paper suggests the acceptance of FIT by clinicians was still low at the time of publishing and that any changes to the national guidelines need intensive support, although reflects attitudes from a relatively early point in the history of using FIT in symptomatic populations.

In summary, further work will be required to engage all areas of the UK to ensure an equivalent and equitable service, and further direct evidence of acceptability of FIT by patients and clinicians needs to be developed.

DISCRIMINATION

We recommend that clinicians actively prevent discrimination at any stage of the diagnostic pathway as symptomatic FIT testing is rolled out, with a focus on equity of access and application to all patients with lower GI symptoms

GRADE of evidence: very low; Strength of recommendation: Strong.

While the data on discrimination in symptomatic FIT are extremely limited, active efforts should be made to avoid discrimination as symptomatic FIT testing is rolled out, with a clear emphasis on equity of access and application.

Data on the role of underutilisation of CRC screening among certain racial and ethnic minorities, age groups and among persons with lower socioeconomic status in the screening literature are well reported[139]; however, data on differences in utilisation for FIT testing in symptomatic patients is very limited. Differential FIT utilisation can occur for a range of reasons: due to inability to perform the test, for example, due to rheumatological or neurological disability preventing fine motor skills to collect the sample; blindness; unwillingness to engage with stool based testing, perhaps due to level of disgust in performing the test, with some evidence from screening that more disgust sensitive individuals may be disinclined to complete any test involving collection of faeces[140]; and subsequent unwillingness to proceed to whole colon examination after a positive FIT result. In an US screening observational study only 43% of FIT positive patient completed colonoscopy by 6 months.[141] Nine per cent (103/1085) of patients with a positive FIT test for CRC symptoms did not proceed to secondary care assessment within 28 days of the test in a study in the NHS (Mr M Abulafi, personal communication 3rd May 2022).

It is also possible that clinicians may choose to use FIT differentially in patients presenting with lower GI symptoms based on their assessment of the pre-test probability for CRC for the patient in front of them, a conscious bias, or equally if GPs feel less confident about discussing the benefits of FIT with patients (OR 2.15, 95% CI 1.46 to 3.16)[138]; however there remains a risk of unconscious bias. If patients perceive medical discrimination, they may be less likely to come forward for screening. In a Californian cohort, women perceiving medical discrimination (racial or ethnic-based) were less likely to be screened for CRC (OR, 0.66; 95% CI 0.64 to 0.69),[142] which might also reduce engagement with FIT-based symptomatic testing.

Translating the data from screening, where the whole population are invited for a test, to scenarios where patients are seeking healthcare for lower GI symptoms is a challenge, which may be exacerbated by whether the assessment is made in primary or secondary care. However interestingly from the screening literature, differences in choice of test occurred over time following changes in CRC screening options by the US Preventive Services Task Force, where when less invasive screening options were available (FIT and multitarget stool DNA tests), they saw increased use of less invasive options.[141] The new widespread availability and promotion of FIT-based testing for symptomatic patients may facilitate access for some groups who were previously unwilling to come forwards for investigation of their lower GI symptoms due to concerns about invasive testing.

For those with dexterity difficulties in performing the test, digital rectal examination to obtain stool for FIT testing appears to offer similar accuracy to home performed tests.[78] This might be combined with point-of-care testing to allow for discussion of an appropriate whole colon examination following a positive test with the clinician to support engagement with downstream testing for CRC in a single consultation.[143]

IMPLEMENTATION

We recommend that FIT, as a diagnostic triage tool, can be implemented safely at primary care level, and that a programme of education be developed to facilitate implementation of FIT in primary care.

GRADE of evidence: very low; Strength of recommendation: Strong.

Most studies of the use FIT in the symptomatic population are essentially studies of diagnostic accuracy. However, FIT is not a diagnostic test for colorectal neoplasia, and even at very low thresholds, sensitivity is not 100%, that is, not all cancers will be detected. Thus, for it to act as an effective means of triaging symptomatic patients for further diagnostic investigation, it is essential that it should be employed as an aid to decision-making against a background of clinical acumen and auxiliary tests, especially an FBC. Furthermore, in order that the impact on referral to secondary care and subsequent diagnostic workload is maximised, it can be argued that the ideal stage in the patient pathway to use FIT is in primary care.

Currently there is a paucity of pragmatic implementation studies of FIT as a diagnostic aid with a view to optimising referral patterns. However, there are some studies that provide useful data.

Mowat and his colleagues[16] have reported on the outcomes of a service development where GPs were encouraged to use FIT in addition to clinical assessment and FBC irrespective of symptoms. The fHb was measured using HM-JACKarc (Kyowa

Medex) with a recommended cut-off of ≥10 µg Hb/g faeces. Anonymised record linkage to the Scottish Cancer Registry was used to find incident cases of CRC. During the study period FIT specimen were submitted for 5422 patients and the positivity at the chosen threshold was 21.9%. Irrespective of FIT result, 2848 patients had an immediate referral to secondary care and 3 with fHb <10 µg/g presented with obstructing CRC shortly after submission of the FIT. Colonoscopy was carried out in 1447 and the prevalence of SBD was 20.5% (95 CRC (6.6%), 133 high-risk adenomas (9.2%) and 68 IBD (4.7%)); this represented 6.6% of patient with an fHb <10 µg/g and 32.3% in those with fHb ≥10 µg/g. There was no immediate referral in 2521 patients 95.3% of whom had fHb <10 µg/g. Four of these (0.2%) were later diagnosed with CRC. The record linkage did not identify any additional CRC cases within a follow-up period of 23–35 months. In the first year of this service, a reduction in referrals of 15.1% was seen.

McSorley and others[31] reported data from three Scottish NHS Boards, where HM-JACKarc FIT kits were employed by GPs as an aid to referral in the same way as Mowat *et al*.[1] In total 4840 patients who had colonoscopy after FIT submission were included. Of 2166 patients (44.7%) with fHb <10 µg Hb/g faeces (µg/g), 14 (0.6%) had a diagnosis of CRC, with the NNS of 155. In the 2675 patients (55.3%) with fHb ≥10 µg/g, there were 252 CRCs found (9.4%) with an NNS of 11. In 705 patients with fHb ≥400 µg/g, 158 (22.4%) had CRC with an NNS of 5. More than 50% of those with CRC and an fHb <10 µg/g had coexisting anaemia.

Chapman *et al*[74] incorporated postal FIT into the CRC 2WW pathway in those without rectal bleeding for a 1-year period. A total of 1106 patients received FIT and 80.9% returned them; 810 patients were investigated and 40 CRCs were found (4.95%). 60.4% of all patients had an FIT result lower than 4 µg/g, and 69.7% had a result of <10. Sixty per cent of patients with CRC had an FIT result of ≥150 µg/g. In five CRCs in patients with an FIT value <10 µg/g there was either anaemia or a palpable rectal mass or the patient was anaemic. An FIT result >10 µg/g was associated with a 97.5% sensitivity and 64.5% specificity for CRC whereas a result >4 µg/g and/or anaemia was 100% sensitive and 45.3% specific for CRC.

Bailey *et al*[9] carried out a service evaluation of GP access to FIT as an aid to CRC diagnosis. Over a 1-year period, there were 5733 FIT results, of which 4082 (71.2%) were <4.0 µg/g, 579 (10.1%) were 4.0–9.9 µg/g, 836 (14.6%) were 10.0–149.9 µg/g and 236 (4.1%) were >150.0 mg µg/g. A 33% rise in urgent referrals was seen during the evaluation. In the 4082 patients with FIT <4.0 µg/g two CRCs were diagnoses. Of all the CRCs 58.4% of those associated with a positive FIT result were early (Stage I and II) and the percentage of CRC diagnoses that arose from an urgent referral rose after introduction of FIT.

Finally, in a study of GPs' attitudes to FIT, Von and his colleagues,[138] conducted prior to higher FIT utilisation during the COVID-19 pandemic, found that only one-third of GPs would prefer to use FIT rather than the current 2WW criteria for referral.

Anecdotal experience from the Thames Valley region, where FIT was rolled out rapidly due to the COVID-19 pandemic suggests that effective communication between clinical commissioning group and cancer alliances with GPs is critical, via webinars and more traditional methods, for example, newssheets. Published evidence was important for many GPs to make practice change, as was the availability formal advice from NHSE (National Health Service England). Oxford was an early adopter of FIT in 2016 and may not be representative as many GPs were already using this technique. When approaching regions that did not have locally available FIT testing embedded, there was considerably more resistance to the move. Clarity on the mechanisms and role of safety netting was also critical in driving engagement. In addition, standardisation of reporting which includes clear instructions about the clinical actionability of FIT results would facilitate interpretation in primary or secondary care.

Further advice about implementation with signposting to existing programmes in available in online supplemental file 2.

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Supplement 1: Methodology

- GDG and extended-Delphi Group
- PICOs
- Systematic review flowchart
- GRADE tables

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PICOs

PICO 1: Diagnostic utility of FIT in patients with a suspicion of CRC

Population	**Intervention**	**Comparisons**	**Outcome**
Patients with signs or symptoms of suspected CRC (CRC) Subgroups: a. Patient factors: i. Age ii. Ethnicity iii. Gender iv. Deprivation v. Geography vi. Smoking	Pathways including FIT testing in **primary care** to: a. triage patients for referral to secondary care (2WW / urgent / routine / safety netting / none) Subgroups: a. FIT Threshold i. Value (ug/g) ii. Single or multiple (e.g. for population subgroup) b. FIT Interpretation	Pathways not including FIT testing in **primary care**. Specialist investigation: i. Direct colonoscopy ii. CT Colonography iii. Flexible sigmoidoscopy iv. Colon Capsule v. Composite of specialist investigations vi. Other Clinical records follow-up: i.6 months ii.12 months	Patient reported outcomes: a. **Critical** for decision making i. Overall survival ii. Disease free survival iii. Progression free survival iv. Morbidity related to tests in those without bowel disease v. Quality of Life b. **Important** for decision making i. Serious adverse effects ii. Time intervals to diagnosis (consultation -> FIT -> referral -> diagnosis -> treatment)

vii. BMI viii. Anticoagulants/antiplatelets ix. Family history x. Previous whole colon investigation xi. Other b. Specific symptoms/signs: i. PR Bleeding ii. Change in bowel habit i. Overall ii. Constipation iii. Diarrhoea iii. Abdominal mass iv. Abdominal pain v. Unexplained Weight loss	i. alone ii. plus clinical assessment iii. plus simple biomarkers iv. plus safety netting protocol v. incorporated into a prediction model c. FIT laboratory platform: i. Individually (OC-Sensor, HM-JACKarc, FOB Gold, other) ii. Combined	iii. 18 months iv. 24 months v. Other	iii. Complications – e,g, physical functioning / incontinence / stoma iv. Recurrence Surrogate/Intermediate outcomes: a. **Critical** for decision making i. Diagnostic accuracy ii. Changes in treatment offered iii. Stage at diagnosis (% stage I & II) iv. Route to diagnosis (all categories) - 2WW referral - Urgent referral

vi. Palpable Rectal mass vii. Anal mass / anal ulceration viii. Other c. Specific blood abnormalities i. IDA ii. Broad anaemia iii. Thrombocytosis iv. Hyper-ferritinaemia v. Other d. Clinically stratified i. Any symptoms/signs of concern ii. High-risk (e.g. NG12 criteria) iii. Low-risk (e.g. DG30 criteria)	Pathways including FIT testing in **secondary care** to: a. counsel patient on decision/need to investigate b. determine choice of investigation (urgent / convert to routine with GP consent) c. select patients for one-stop investigation (endoscopy with dedicated radiology staging slots) Subgroups: a. FIT Threshold i. Value (ug/g)	Pathways not including FIT testing in **secondary care**. Specialist investigation: i. Direct colonoscopy ii. CT Colonography iii. Flexible sigmoidoscopy iv. Colon capsule v. Composite of specialist investigations vi. Other Clinical records follow-up: i. 6 months ii. 12 months iii. 18 months iv. 24 months v. Other	- Routine referral - Emergency presentation v. Number needed to (scope / CTC) to detect one cancer vi. Patient acceptability / reassurance b. **Important** for decision making i. Improved diagnostic pathway elements ii. Length of stay in hospital iii. Clinician acceptability iv. Number of tests performed per patient

	ii. Single or multiple (e.g. for population subgroup) b. FIT Interpretation i. alone ii. plus clinical assessment iii. plus simple biomarkers vi. plus safety netting protocol iv. incorporated into a prediction model c. FIT laboratory platform: i. Individually (OC-Sensor, HM-JACKarc, FOB Gold, other)		

	ii. Combined		

PICO 2: What mechanisms may be employed to avoid delayed diagnosis in patients with FIT negative CRC?

Population	**Intervention**	**Comparison**	**Outcome**
Patients with a negative FIT Patients who do not return FIT Subgroups: a. Patient factors: i. Age ii. Ethnicity iii. Gender iv. Deprivation v. Geography vi. Previous whole colon investigation b. Ongoing / no ongoing symptoms c. Referred / not referred.	Referral (urgent / routine) in selected subgroups (demographics / symptoms /blood results). Repeat FIT testing (frequency and interval) Safety netting (as defined by study) Clinical assessment Use of other simple tests i. Platelets ii. Haemoglobin iii. MCV iv. Ferritin	Watch and wait in primary care No safety netting Single FIT test An alternative intervention	Patient reported outcomes: a. **Critical** for decision making i. Overall survival ii. Disease free survival iii. Progression free survival iv. Morbidity related to tests in those without bowel disease v. Quality of Life b. **Important** for decision making i. Serious adverse effects ii. Time to diagnosis (consultation -> FIT -> referral -> diagnosis -> treatment) iii. Complications – e,g, physical functioning / incontinence / stoma iv. Recurrence Surrogate/Intermediate Outcomes:

	v. CRP vi. Other		c. **Critical** for decision making i. Diagnostic accuracy ii. Changes in treatment offered iii. Stage at diagnosis iv. Route to diagnosis (all categories) - 2WW referral - Urgent referral - Routine referral - Emergency presentation v. Number needed to (scope / CTC) to detect one cancer vi. Patient acceptability / reassurance d. **Important** for decision making i. Improved diagnostic pathway elements ii. Length of stay in hospital iii. Clinician acceptability iv. Number of tests performed per patient

PICO 3: FIT and equality and access to care

1) What is the acceptability of FIT in patients with suspected CRC symptoms and their treating clinicians?
2) How can we avoid discriminating against certain populations in this guideline?
3) What lessons may be learned from implementation programmes of FIT in symptomatic populations?

May need to develop non-PICO model for this topic

Population	**Intervention**	**Comparison**	**Outcome**
Patients with symptoms of suspected CRC ○ Subgroups: - Patient - Age, ethnicity, gender, language, deprivation - Learning disability - Hearing or sight impaired	FIT testing ○ Qualitative outcomes ○ Uptake in subgroup populations ○ Implementation	Direct – Specialist investigation: i. Direct colonoscopy ii. CT Colonography iii. Flexible sigmoidoscopy iv. Colon Capsule v. Composite of specialist investigations vi. Other	PRO • Critical for decision making i. Overall survival ii. Disease free survival iii. Progression free survival iv. Morbidity (to be decided what is included) **v. Quality of Life** • Important for decision making i. Serious adverse effects ii. Time to diagnosis

- Accessibility other e.g. housebound, travel - Other physical conditons - Symptoms: High vs low-risk			iii. Physical functioning / incontinence / stoma iv. Recurrence Unimportant for decision making v. Costs, # of colonoscopies vi. Adverse effects including psychological vii. Satisfaction Intermediates • Critical for decision making • Diagnostic accuracy • Changes in treatment offered • Stage at diagnosis • Route to diagnosis (all categories) • Number needed to (colono)scope / CTC

			• Patient acceptability (combine with reassurance) • Important for decision making • Improved diagnostic pathway elements • Length of stay in hospital • Reassurance / time to reassurance / time to diagnostic resolution • Clinician acceptability • Number of tests performed Critical: • CRC diagnostic accuracy • Time to diagnosis • Earlier diagnosis (stage shift) Important:

			• Prioritising investigations • Morbidity of interventions • Reduced CRC Morbidity • Develop patient pathway to diagnosis Lower importance • Predicted resource impact • SBD: Polyps – advanced / non-advanced • Other SBD

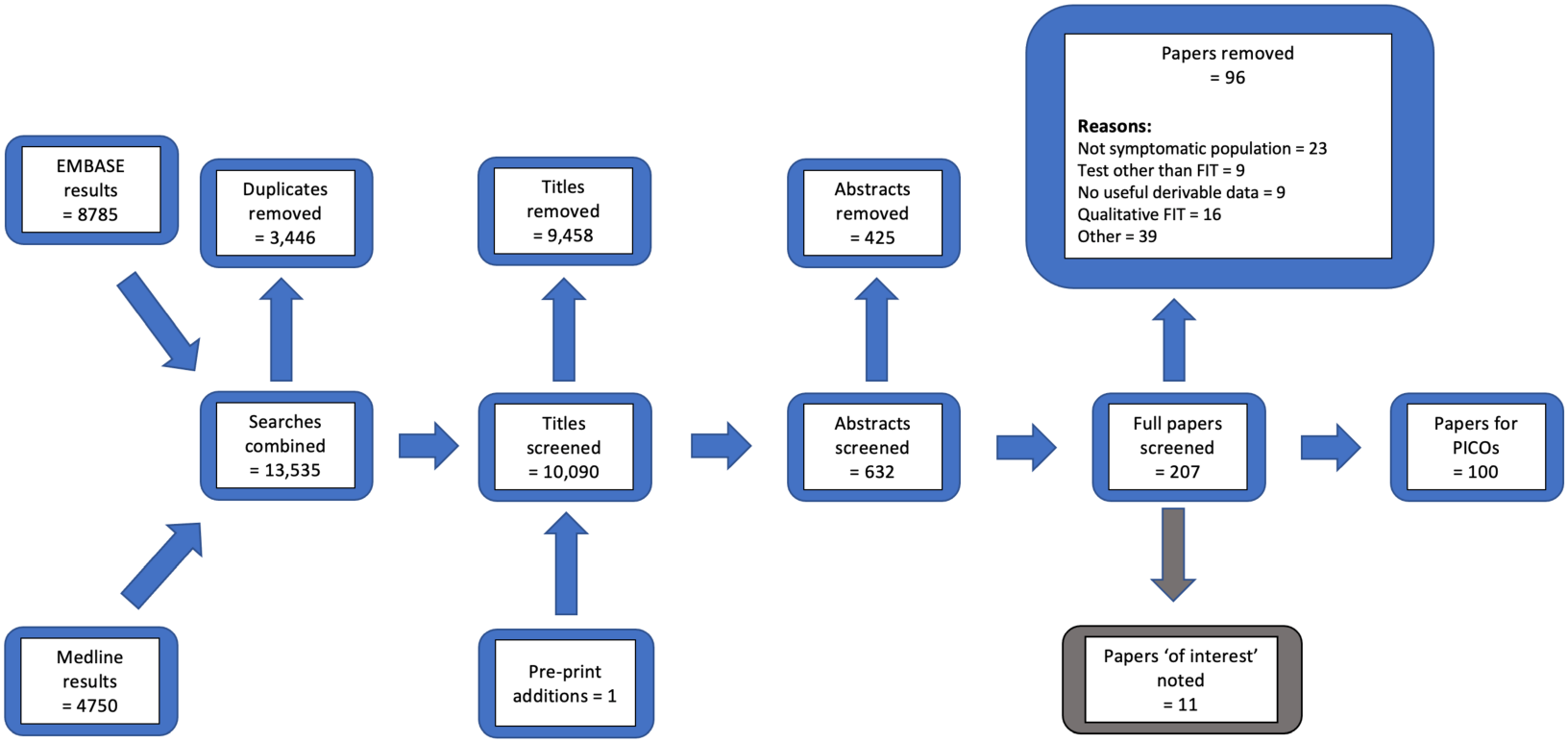

Figure S1: Flowchart of systematic review of evidence

GRADE Tables

Table 1: Should Faecal immunochemical test be used to diagnose colorectal cancer in patients with all symptoms (NG12, DG30 or NC)?

Sensitivity	0.90 (95% CI: 0.88 to 0.92)
Specificity	0.76 (95% CI: 0.71 to 0.80)

Prevalences			
	4.2%	1.1%	13.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of4.2%	pre-test probability of1.1%	pre-test probability of13.6%	
True positives (patients with colorectal cancer)	15 studies 35782 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	none	38 (37 to 39)	10 (10 to 10)	122 (120 to 125)	⊕◯◯◯ Very low[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15]
False negatives (patients incorrectly classified as not								4 (3 to 5)	1 (1 to 1)	14 (11 to 16)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of4.2%	pre-test probability of1.1%	pre-test probability of13.6%	
having colorectal cancer)											
True negatives (patients without colorectal cancer)	15 studies 35782 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	none	728 (680 to 766)	752 (702 to 791)	657 (613 to 691)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having colorect								230 (192 to 278)	237 (198 to 287)	207 (173 to 251)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of4.2%	pre-test probability of1.1%	pre-test probability of13.6%	
al cancer)											

Explanations:

a. Studies were judged at a high risk of bias in patient selection.

b. Results based on indirect comparisons from different studies; direct evidence about impact on patient-important outcomes

c. Significant heterogeneity detected

Footnote: CoE = certainty of evidence

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Table 2: Flexible sigmoidoscopy compared to FIT (if negative) for referral of patients with persistent / recurrent rectal bleeding
Setting: Secondary care

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Under-detection of CRC (assessed with: FIT)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1	observational studies	serious[a]	not serious	serious[b]	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect	We recommend referral of patients with persistent / recurrent rectal bleeding for flexible sigmoidoscopy if FIT is negative. In patients with rectal bleeding and undetectable f-Hb the use of flexible sigmoidoscopy can reduce the probability of undetected CRC to 0.03%.	⨁◯◯◯ Very low[1]	CRITICAL

CI: confidence interval

Explanations

a. D'Souza was judged at a high risk of bias in patient selection.

b. Direct evidence about impact on patient-important outcomes was missing

c. Wide confidence intervals for sensitivity in NRB for >10

References

1.Hicks, G, D'Souza, N, Georgiou Delisle, T, Chen, M, Benton, S C, Abulafi, M. Using the faecal immunochemical test in patients with rectal bleeding: evidence from the NICE FIT study. Colorectal Disease; 2021.

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Table 3: Should FIT threshold of ≥10µg vs. be used for be used to diagnose in referral for CRC investigation?

Sensitivity	0.91 (95% CI: 0.85 to 0.94)
Specificity	0.71 (95% CI: 0.57 to 0.82)

Prevalences	1.1%	0.8%	1.8%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1.1%	pre-test probability of0.8%	pre-test probability of1.8%	
True positives (patients with)	4 studies 12141 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious[b]	serious[c]	not serious	none	10 (9 to 10)	7 (7 to 8)	16 (15 to 17)	⊕◯◯◯ Very low[1,2,3,4]
False negatives (patients incorrectly classified as not having)								1 (1 to 2)	1 (0 to 1)	2 (1 to 3)	
True negatives (patients without)	4 studies 12141 patients	cross-sectional (cohort type	serious [a]	serious[b]	serious[c]	not serious	none	702 (564 to 811)	704 (565 to 813)	697 (560 to 805)	⊕◯◯◯ Very low

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1.1%	pre-test probability of0.8%	pre-test probability of1.8%	
False positives (patients incorrectly classified as having)		accuracy study)						287 (178 to 425)	288 (179 to 427)	285 (177 to 422)	

Explanations

a. Studies were judged at a high risk of bias in patient selection.

b. Results based on indirect comparisons from different studies; direct evidence about impact on patient-important outcomes

c. Significant heterogeneity detected

Footnote: CoE = certainty of evidence

References

1.Chapman, C, Bunce, J, Oliver, S, Ng, O, Tangri, A, Rogers, R, Logan, R F, Humes, D J, Banerjea, A. Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. BJS Open; 2019.

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Table 4: Should OC-sensor vs. HM JACK-arc be used to diagnose CRC in patients with all symptoms (NG12, DG30 or NC)?

OC-sensor		HM JACK-arc	
Sensitivity	0.90 (95% CI: 0.86 to 0.93)	Sensitivity	0.90 (95% CI: 0.87 to 0.92)
Specificity	0.74 (95% CI: 0.68 to 0.79)	Specificity	0.78 (95% CI: 0.69 to 0.85)

Prevalences	4.2%	1.1%	13.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.2%		pre-test probability of1.1%		pre-test probability of13.6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	OC-sensor	HM JACK-arc	OC-sensor	HM JACK-arc	OC-sensor	HM JACK-arc	
True positives (patients with CRC)	13 studies 34813 patients	cross-sectional (cohort type accura	not serious	serious[a]	serious[b]	not serious	none	38 (36 to 39)	38 (37 to 39)	10 (9 to 10)	10 (10 to 10)	122 (117 to 126)	122 (118 to 125)	⊕⊕◯◯ Low[1,2,3,4,5,6,7,8,9,10,11,12,13]
								0 fewer TP in OC-sensor		**0 fewer TP in OC-sensor**		**0 fewer TP in OC-sensor**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.2%		pre-test probability of1.1%		pre-test probability of13.6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	OC-sensor	HMJACK-arc	OC-sensor	HMJACK-arc	OC-sensor	HMJACK-arc	
False negatives (patients incorrectly classified as not having CRC)		cy study)						4 (3 to 6)	4 (3 to 5)	1 (1 to 2)	1 (1 to 1)	14 (10 to 19)	14 (11 to 18)	
								0 fewer FN in OC-sensor		**0 fewer FN in OC-sensor**		**0 fewer FN in OC-sensor**		
True negatives (patients without CRC)	13 studies 34813 patients	cross-sectional (cohort type accura	not serious	serious[a]	serious[b]	not serious	none	709 (651 to 757)	747 (661 to 814)	732 (673 to 781)	771 (682 to 841)	639 (588 to 683)	674 (596 to 734)	⊕⊕◯◯ Low
								38 fewer TN in OC-sensor		**39 fewer TN in OC-sensor**		**35 fewer TN in OC-sensor**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.2%		pre-test probability of1.1%		pre-test probability of13.6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	OC-sensor	HMJACK-arc	OC-sensor	HMJACK-arc	OC-sensor	HMJACK-arc	
False positives (patients incorrectly classified as having CRC)		cy study)						249 (201 to 307)	211 (144 to 297)	257 (208 to 316)	218 (148 to 307)	225 (181 to 276)	190 (130 to 268)	
								38 more FP in OC-sensor		**39 more FP in OC-sensor**		**35 more FP in OC-sensor**		

Explanations

a. Results based on indirect comparisons from different studies

b. There was high amount of heterogeneity detected.

Footnote: CoE = certainty of evidence

References

1.Chapman, C, Thomas, C, Morling, J, Tangri, A, Oliver, S, Simpson, J A, Humes, D J, Banerjea, A. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham. Colorectal Disease; 2020.

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13.Morales Arraez, D E, Hernandez, G, Carrillo, M, Adrian, Z, Gimeno, A Z, Quintero, E. Role of faecal immunochemical testing in the diagnostic workup of patients with iron deficiency anaemia. United European Gastroenterology Journal; 2018.

Table 5: Should FOB Gold vs. QuikRead go be used to diagnose CRC in in patients with all symptoms (NG12, DG30 or NC)?

FOB Gold		QuikRead go	
Sensitivity	0.94 (95% CI: 0.81 to 0.99)	Sensitivity	0.92 (95% CI: 0.64 to 0.99)
Specificity	0.75 (95% CI: 0.71 to 0.78)	Specificity	0.77 (95% CI: 0.71 to 0.82)

Prevalences	5.1%	5%	5.3%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of5.1%		pre-test probability of5%		pre-test probability of5.3%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FOB Gold	QuikRead go	FOB Gold	QuikRead go	FOB Gold	QuikRead go	
True positives (patients with CRC)	1 studies 727 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	none	48 (41 to 50)	47 (33 to 50)	47 (41 to 50)	46 (32 to 50)	50 (43 to 52)	49 (34 to 52)	⊕◯◯◯ Very low[1]
								1 more TP in FOB Gold		**1 more TP in FOB Gold**		**1 more TP in FOB Gold**		
False negatives								3 (1 to 10)	4 (1 to 18)	3 (0 to 9)	4 (0 to 18)	3 (1 to 10)	4 (1 to 19)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of5.1%		pre-test probability of5%		pre-test probability of5.3%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FOB Gold	QuikRead go	FOB Gold	QuikRead go	FOB Gold	QuikRead go	
(patients incorrectly classified as not having CRC)								**1 fewer FN in FOB Gold**		**1 fewer FN in FOB Gold**		**1 fewer FN in FOB Gold**		
True negatives (patients without CRC)	1 studies 727 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	serious	none	712 (674 to 740)	731 (674 to 778)	712 (675 to 741)	731 (675 to 779)	710 (672 to 739)	729 (672 to 777)	⊕◯◯◯ Very low
								19 fewer TN in FOB Gold		**19 fewer TN in FOB Gold**		**19 fewer TN in FOB Gold**		
False positives (patients								237 (209 to	218 (171 to 275)	238 (209 to	219 (171 to 275)	237 (208 to	218 (170 to 275)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of5.1%		pre-test probability of5%		pre-test probability of5.3%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FOB Gold	QuikRead go	FOB Gold	QuikRead go	FOB Gold	QuikRead go	
incorrectly classified as having CRC)								275)		275)		275)		
								19 more FP in FOB Gold		**19 more FP in FOB Gold**		**19 more FP in FOB Gold**		

Explanations

a. Tsapournas 2020 was judged at a high risk of bias in patient selection.

b. Results based on indirect comparisons from different studies

c. There was high amount of heterogeneity detected.

Footnote: CoE = certainty of evidence

References

1.Navarro, M, Hijos, G, Sostres, C, Lue, A, Puente-Lanzarote, J J, Carrera-Lasfuentes, P, Lanas, A. Reducing the Cut-Off Value of the Fecal Immunochemical Test for Symptomatic Patients Does Not Improve Diagnostic Performance. Frontiers in Medicine; 2020.

Table 6: Should CT colonography be preferred over colonoscopy for patients with non-specific symptoms including abdominal pain or weight loss?

Patient or population: patients with non-specific symptoms including abdominal pain or weight loss
Setting: 2WW CRC pathway
Intervention: Is CT colonography preferred
Comparison: colonoscopy

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Patients' preference (Preference)	For patients recommended whole colon investigation as part of a 2WW CRC pathway, CTC is equivalent to colonoscopy for detection of CRC; and use of CTC can be determined by local teams according to audited performance, capacity and experience	9822 (1 observational study)	⨁⨁◯◯ Low[1,2,a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Study was judged to be at a high risk of bias.

References

1.D'Souza N, Delisle TG,Chen M,Benton S,Abulafi M,NICE FIT Steering Committee. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway; a diagnostic accuracy study. Gut; 2020.

2.Delisle, T G, D'Souza, N, Davies, B, Ward, H, Abulafi, M. Patient acceptability of a home colorectal cancer rule out test. British Journal of Surgery; 2020.

Table 7: Should FIT be used to diagnose CRC in younger patients (<50)?

Sensitivity	0.81 to 0.93
Specificity	0.83 to 0.88

Prevalences	2.7%	1.5%	3.9%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2.7%	pre-test probability of1.5%	pre-test probability of3.9%	
True positives (patients with CRC)	2 studies 9969 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious[b]	not serious	not serious	none	22 to 25	12 to 14	32 to 36	⊕⊕◯◯ Low[1,2]
False negatives (patients incorrectl								2 to 5	1 to 3	3 to 7	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2.7%	pre-test probability of1.5%	pre-test probability of3.9%	
y classified as not having CRC)											
True negatives (patients without CRC)	2 studies 9969 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious[b]	not serious	not serious	none	808 to 856	818 to 867	798 to 846	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having CRC)								117 to 165	118 to 167	115 to 163	

Explanations

a. High risk of bias in patient selection

b. Results based on indirect comparisons from different studies

Footnote: CoE = certainty of evidence

References

1.Lue, A, Hijos, G, Sostres, C, Perales, A, Navarro, M, Barra, M V, Mascialino, B, Andalucia, C, Puente, J J, Lanas, A, Gomollon, F. The combination of quantitative faecal occult blood test and faecal calprotectin is a cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology. Therapeutic Advances in Gastroenterology; 2020.

2.D'Souza, N, Monahan, K, Benton, S C, Wilde, L, Abulafi, M, Group, Nice Fit Steering. Finding the needle in the haystack: the diagnostic accuracy of the faecal immunochemical test for colorectal cancer in younger symptomatic patients. Colorectal Disease; 2021.

Table 8: FIT compared to no test or no-return for risk of CRC
Patient or population: risk of CRC
Setting: Various
Intervention: FIT
Comparison: no test or no-return

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Adherence (Adherence) assessed with: Questionnaire/survey	We recommend that GPs should be advised that in a symptomatic patient with no recent FIT result (through lack of return of the kit or sample failure) evaluation of CRC risk is likely to be suboptimal. This is likely to be of an order greater than failing to consider well known “alarm” symptoms such as rectal bleeding or change in bowel habit. We recommend that patients who refuse to return a FIT test should be counselled that the absence of a result may impair their responsible clinician’s ability to correctly assess their risk of CRC and take appropriate action to address this.	(0 studies)	-

Table 8: FIT compared to no test or no-return for risk of CRC
Patient or population: risk of CRC
Setting: Various
Intervention: FIT
Comparison: no test or no-return

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 9: Should FIT (HM-JACKarc) be used to diagnose CRC in similar in both high (NG12) and low risk (DG30) symptomatic patients (in any setting at the >10 cut-off, Tier 1)?

FIT (HM-JACKarc) DG30		FIT (HM-JACKarc) NG12	
Sensitivity	0.88 (95% CI: 0.78 to 0.95)	Sensitivity	0.89 (95% CI: 0.82 to 0.93)
Specificity	0.88 (95% CI: 0.87 to 0.89)	Specificity	0.81 (95% CI: 0.79 to 0.82)

Prevalences	4.6%	3.3%	6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.6%		pre-test probability of3.3%		pre-test probability of6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	
True positives (patients with CRC)	4 studies 11464 patients	cross-sectional (cohort type accuracy study)	serious[1,2,3,4,a]	serious[b]	serious[c]	not serious	none	40 (36 to 44)	41 (38 to 43)	29 (26 to 31)	29 (27 to 31)	53 (47 to 57)	53 (49 to 56)	⊕◯◯◯ Very low
								1 fewer TP in FIT (HM-JACKarc) DG30		**0 fewer TP in FIT (HM-JACKarc) DG30**		**0 fewer TP in FIT (HM-JACKarc) DG30**		
False negatives (patients incorrec								6 (2 to 10)	5 (3 to 8)	4 (2 to 7)	4 (2 to 6)	7 (3 to 13)	7 (4 to 11)	
								1 more FN in FIT (HM-JACKarc) DG30		**0 fewer FN in FIT (HM-JACKarc) DG30**		**0 fewer FN in FIT (HM-JACKarc) DG30**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.6%		pre-test probability of3.3%		pre-test probability of6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	
tly classified as not having CRC)														
True negatives (patients without CRC)	4 studies 11464 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	none	840 (830 to 849)	773 (754 to 782)	851 (841 to 861)	783 (764 to 793)	827 (818 to 837)	761 (743 to 771)	⊕◯◯◯ Very low
								67 more TN in FIT (HM-JACKarc) DG30		**68 more TN in FIT (HM-JACKarc) DG30**		**66 more TN in FIT (HM-JACKarc) DG30**		
False positives (patient								114 (105 to 124)	181 (172 to 200)	116 (106 to 126)	184 (174 to 203)	113 (103 to 122)	179 (169 to 197)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of4.6%		pre-test probability of3.3%		pre-test probability of6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	FIT (HM-JACKarc) DG30	FIT (HM-JACKarc) NG12	
s incorrectly classified as having CRC)								**67 fewer FP in FIT (HM-JACKarc) DG30**		**68 fewer FP in FIT (HM-JACKarc) DG30**		**66 fewer FP in FIT (HM-JACKarc) DG30**		

Explanations

a. Farrugia 2020 was judged to be at a high risk of bias for flow and timing; D'Souza 2020 was judged to be at a high risk of bias for patient selection.

b. Results based on indirect comparisons from different studies; direct evidence about impact on patient-important outcomes missing.

c. Significant heterogeneity for sensitivity detected.

Footnote: CoE = certainty of evidence

References

1.D'Souza, N., Georgiou Delisle, T., Chen, M., Benton, S., Abulafi, M.. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: A diagnostic accuracy study. Gut; 2021.

2.Chapman, C. J., Banerjea, A., Humes, D. J., Allen, J., Oliver, S., Ford, A., Hardy, K., Djedovic, N., Logan, R. F., Morling, J. R.. Choice of faecal immunochemical test matters: comparison of OC-Sensor and HM-JACKarc, in the assessment of patients at high risk of colorectal cancer. Clin Chem Lab Med; Oct 29 2020.

3.D'Souza N, Delisle TG,Chen M,Benton S,Abulafi M,NICE FIT Steering Committee. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway; a diagnostic accuracy study. Gut; 2020.
4.Farrugia, A, Widlak, M, Evans, C, Smith, S C, Arasaradnam, R. Faecal immunochemical testing (FIT) in symptomatic patients: What are we missing?. Frontline Gastroenterology; 2020.

Table 10: Should FIT (OC-sensor) be used to diagnose CRC in in patients with rectal bleeding (in primary care at >10 cut-off)?

Sensitivity	0.96 (95% CI: 0.80 to 0.99)
Specificity	0.38 (95% CI: 0.33 to 0.43)

Prevalences	5.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of5.6%	
True positives (patients with CRC)	1 studies 462 patients	cross-sectional (cohort type accuracy study)	serious[1,a]	serious[b]	not serious	serious[c]	none	54 (45 to 55)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having CRC)								2 (1 to 11)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of5.6%	
True negatives (patients without CRC)	1 studies 462 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	serious[c]	none	359 (312 to 406)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having CRC)								585 (538 to 632)	

Explanations

a. Mowat/Digby was judged to be at a high risk of bias for flow and timing; and a high risk of bias for patient selection.

b. direct evidence about impact on patient-important outcomes is missing.

c. Wide confidence intervals

Footnote: CoE = certainty of evidence

References

1.Mowat, C., Digby, J., Strachan, J. A., Wilson, R., Carey, F. A., Fraser, C. G., Steele, R. J.. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. Gut; Sep 2016.

Table 11: Should FIT (HM-JACKarc) be used to diagnose CRC in iron deficiency anaemia?

Sensitivity	1.00 (95% CI: 0.89 to 1.00)
Specificity	0.81 (95% CI: 0.77 to 0.85)

Prevalences	3.3%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.3%	pre-test probability of0%	pre-test probability of0%	
True positives (patients with CRC)	1 studies 479 patients	cross-sectional (cohort type accuracy study)	serious[1, a]	serious[b]	not serious	serious[c]	none	33 (29 to 33)	0 (0 to 0)	0 (0 to 0)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having CRC)								0 (0 to 4)	0 (0 to 0)	0 (0 to 0)	
True negatives (patients without CRC)	1 studies 479 patients	cross-sectional (cohort type	serious[a]	serious[b]	not serious	serious[c]	none	783 (745 to 822)	810 (770 to 850)	810 (770 to 850)	⊕◯◯◯ Very low

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.3%	pre-test probability of0%	pre-test probability of0%	
False positives (patients incorrectly classified as having CRC)		accuracy study)						184 (145 to 222)	190 (150 to 230)	190 (150 to 230)	

Explanations

a. D'Souza 2021 was judged to be at a high risk of bias for patient selection.

b. direct evidence about impact on patient-important outcomes is missing

c. Wide confidence intervals for sensitivity and specificity

Footnote: CoE = certainty of evidence

References

1.D'Souza, N, Delisle, T G, Chen, M, Benton, S C, Abulafi, M, Committee, Nice Fit Steering. Faecal immunochemical testing in symptomatic patients to prioritize investigation: diagnostic accuracy from NICE FIT Study. British Journal of Surgery; 2021.

Table 12: Should FIT (OC-sensor) be used to diagnose CRC in in those with isolated change in bowel habits?

Sensitivity	0.88 (95% CI: 0.79 to 0.95)
Specificity	0.80 (95% CI: 0.79 to 0.81)

Prevalences	1.2%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1.2%	
True positives (patients with CRC)	1 study 5818 patients	cross-sectional (cohort type accuracy study)	serious[1,a]	serious[b]	not serious	serious[c]	publication bias strongly suspected[d]	11 (9 to 11)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having CRC)								1 (1 to 3)	
True negatives (patients without CRC)	1 study 5818 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	serious[c]	publication bias strongly suspected[d]	790 (781 to 800)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having CRC)								198 (188 to 207)	

Explanations

a. Khasawneh 2020 was judged to be at an unclear risk of bias.

b. direct evidence about impact on patient-important outcomes is missing.

c. Wide confidence intervals for sensitivity

d. Results based on a single study
Footnote: CoE = certainty of evidence

References
1.Khasawneh, F, Osborne, T, Stephenson, J, Barnes, D, Seehra, J, Danaher, P, Jones, J, Singh, B. Faecal immunochemical testing is a cost-effective way to stratify symptomatic patients for urgent straight to test investigation. Colorectal Disease; 2020.

Table 13: Should FIT (OC-sensor) be used to diagnose CRC in in patients with CIBH or RB at thresholds >4 to >10 in primary care?

Sensitivity	0.91 to 0.96
Specificity	0.38 to 0.69

Prevalences	0%	1.2%	5.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	pre-test probability of1.2%	pre-test probability of5.6%	
True positives (patients with CRC)	2 studies 6280 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	none	0 to 0	11 to 12	51 to 54	⊕◯◯◯ Very low[1,2]
False negatives (patients incorrectl								0 to 0	0 to 1	2 to 5	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	pre-test probability of1.2%	pre-test probability of5.6%	
y classified as not having CRC)											
True negatives (patients without CRC)	2 studies 6280 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious[b]	serious[c]	not serious	none	380 to 690	375 to 682	359 to 651	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having CRC)								310 to 620	306 to 613	293 to 585	

Explanations

a. Khasawneh 2020 was judged to be at an unclear risk of bias in all domains.

b. Results based on indirect comparisons from different studies; direct evidence about impact on patient-important outcomes is missing

c. Significant heterogeneity detected for both sensitivity and specificity

Footnote: CoE = certainty of evidence

References
1.Khasawneh, F, Osborne, T, Stephenson, J, Barnes, D, Seehra, J, Danaher, P, Jones, J, Singh, B. Faecal immunochemical testing is a cost-effective way to stratify symptomatic patients for urgent straight to test investigation. Colorectal Disease; 2020.
2.Digby, J, Strachan, J A, McCann, R, Steele, R J C, Fraser, C G, Mowat, C. Measurement of faecal haemoglobin with a faecal immunochemical test can assist in defining which patients attending primary care with rectal bleeding require urgent referral. Annals of Clinical Biochemistry; 2020.

Table 14: Should FIT in primary care vs. FIT in secondary care be used to diagnose CRC in adults with lower gastrointestinal signs or symptoms (at >10) and in all symptoms (NG12, DG30 and NC)?

FIT in primary care		FIT in secondary care	
Sensitivity	0.91 (95% CI: 0.85 to 0.94)	Sensitivity	0.91 (95% CI: 0.88 to 0.93)
Specificity	0.71 (95% CI: 0.57 to 0.82)	Specificity	0.79 (95% CI: 0.74 to 0.83)

Prevalences	5.2%	1.2%	13.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of5.2%		pre-test probability of1.2%		pre-test probability of13.6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FIT in primary care	FIT in secondary care	FIT in primary care	FIT in secondary care	FIT in primary care	FIT in secondary care	
True positives (patients with CRC)	13 studies 34357 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	strong association	47 (44 to 49)	47 (46 to 48)	11 (10 to 11)	11 (11 to 11)	124 (116 to 128)	124 (120 to 126)	⊕⊕◯◯ Low[1,2,3,4,5,6,7,8,9,10,11,12,13]
								0 fewer TP in FIT in primary care		**0 fewer TP in FIT in primary care**		**0 fewer TP in FIT in primary care**		
False negatives (patients incorrectly classified as not having CRC)								5 (3 to 8)	5 (4 to 6)	1 (1 to 2)	1 (1 to 1)	12 (8 to 20)	12 (10 to 16)	
								0 fewer FN in FIT in primary care		**0 fewer FN in FIT in primary care**		**0 fewer FN in FIT in primary care**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of5.2%		pre-test probability of1.2%		pre-test probability of13.6%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	FIT in primary care	FIT in secondary care	FIT in primary care	FIT in secondary care	FIT in primary care	FIT in secondary care	
True negatives (patients without CRC)	13 studies 34357 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	strong association	673 (540 to 777)	749 (702 to 787)	701 (563 to 810)	781 (731 to 820)	613 (492 to 708)	683 (639 to 717)	⊕⊕◯◯ Low
								76 fewer TN in FIT in primary care		**80 fewer TN in FIT in primary care**		**70 fewer TN in FIT in primary care**		
False positives (patients incorrectly classified as having CRC)								275 (171 to 408)	199 (161 to 246)	287 (178 to 425)	207 (168 to 257)	251 (156 to 372)	181 (147 to 225)	
								76 more FP in FIT in primary care		**80 more FP in FIT in primary care**		**70 more FP in FIT in primary care**		

Explanations

a. Studies were judged at a high risk of bias in patient selection e.g., McSorley 2020, Mowat 2016.

b. Results based on indirect comparisons from different studies; direct evidence about impact on patient-important outcomes is missing

c. Significant heterogeneity detected for specificity

Footnote: CoE = certainty of evidence

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Question: Should FIT be used to diagnose CRC in aspirin users ?

Sensitivity	0.88 (95% CI: 0.75 to 0.95)
Specificity	0.66 (95% CI: 0.62 to 0.71)

Prevalence	10.5%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10.5%	
True positives (patients with CRC)	1 study 485 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	92 (79 to 100)	⊕◯◯◯ Very low
False negatives (patients incorrectly								13 (5 to 26)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10.5%	
classified as not having CRC)									
True negatives (patients without CRC)	1 study 485 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	591 (555 to 635)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having CRC)								304 (260 to 340)	

Explanations

a. Poor representativeness of the population.

b. Wide confidence intervals; small sample <500 participants

c. Results based on a single study

References:

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Question: Should FIT be used to diagnose CRC in females in secondary care (threshold: ≥10 µg Hb/g)?

Sensitivity	0.76 to 0.88
Specificity	0.82 to 0.85

Prevalences	1.1%	4.5%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.1%	pre-test probability of 4.5%	
True positives (patients with CRC)	2 studies 21435 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	not serious	none	8 to 10	34 to 40	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having CRC)								1 to 3	5 to 11	
True negatives (patients without CRC)	2 studies 21435 patients	cross-sectional (cohort type	serious[a]	serious[b]	not serious	not serious	none	811 to 841	783 to 812	⨁⨁◯◯ Low

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.1%	pre-test probability of 4.5%	
False positives (patients incorrectly classified as having CRC)		accuracy study)						148 to 178	143 to 172	

Explanations

a. High risk of bias in patient selection and index test in Khan 2020.

b. Results based on indirect comparisons from different studies

References

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[2] Khan AA, Klimovskij M, Harshen R. Accuracy of faecal immunochemical testing in patients with symptomatic colorectal cancer. *BJS Open* 2020;4(6):1180-1188.

Question: Should FIT be used to diagnose CRC in males in secondary care (threshold: ≥10 µg Hb/g)?

Sensitivity	0.91 to 0.95
Specificity	0.79 to 0.80

Prevalences	2.3%	5.9%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2.3%	
True positives (patients with CRC)	2 studies 18168 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	not serious	none	21 to 22	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having CRC)								1 to 2	
True negatives (patients without CRC)	2 studies 18168 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	not serious	none	772 to 782	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having CRC)								195 to 205	

Explanations

a. High risk of bias in patient selection and index test in Khan 2020.

b. Results based on indirect comparisons from different studies.

References

[1] Pin-Vieito N, Garcia Nimo L, Bujanda L, Roman Alonso B, Gutierrez-Stampa MA, Aguilar-Gama V, et al. Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study. *United European Gastroenterology Journal* 2021;9(2):256-267.

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Question: Should FIT be used to diagnose CRS in aspirin non-users?

Sensitivity	0.92 (95% CI: 0.88 to 0.95)
Specificity	0.71 (95% CI: 0.69 to 0.73)

Prevalence	11.6%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of11.6%	
True positives (patients with CRS)	1 study 2567 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	107 (102 to 110)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having CRS)								9 (6 to 14)	
True negatives (patients without CRS)	1 study 2567 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	628 (610 to 645)	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having CRS)								256 (239 to 274)	

Explanations

a. Poor representativeness of the population.

b. Results based on a single study.

References:

[1] Bujanda L, Sarasqueta C, Vega P, Salve M, Quintero E, Alvarez-Sanchez V, et al. Effect of aspirin on the diagnostic accuracy of the faecal immunochemical test for colorectal advanced neoplasia. *United European Gastroenterol J* 2018;6(1):123-130.

GRADE Tables

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)

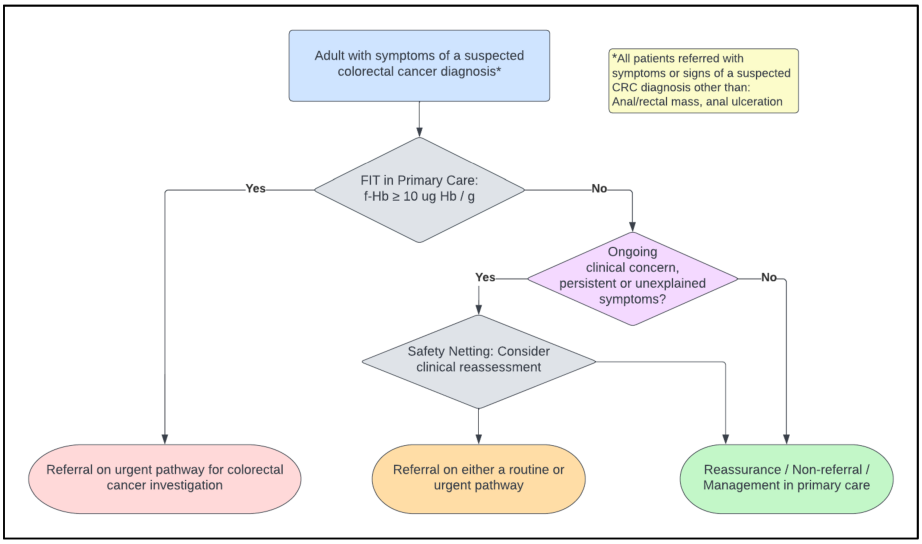

Figure 1: Pathway for Use of FIT in Patients with Signs or Symptoms Raising Suspicion of Colorectal Cancer (CRC) (including those with rectal bleeding, and iron deficiency anaemia).

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

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

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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)?

- 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.

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.

Faecal Immunochemical Testing (FIT) in Patients with Signs or Symptoms of Suspected Colorectal Cancer (CRC): A Joint Guideline from The Association of Coloproctology of Great Britain & Ireland (ACPGBI) and the British Society of Gastroenterology (BSG).

Lay Summary

Bowel symptoms are common and people frequently attend their GP to be assessed. Fortunately for the majority of people, bowel symptoms may be due to a change in the function of the bowel in response to diet and other factors affecting their environment. However, a small number of people with bowel symptoms will have a more serious underlying cause which may include a tumour of the bowel.

To help GPs to identify patients who need further investigation for a suspected bowel tumour, a new test has been introduced. This is called the FIT Test (Faecal Immunochemical Test). The FIT Test is a simple test which patients can do themselves and it tests for tiny amounts of blood in the poo, which can help determine if further tests are needed.

Why have these Guidelines been written?

The FIT test is a relatively new test, so these Guidelines have been written to provide a framework for using the FIT test in the best way. These Guidelines are written primarily to guide the use of FIT testing by Health Professionals and include information on:

- The symptoms and signs that should be assessed by FIT testing
- Where FIT testing should be done
- How a patient should be managed if the FIT test level is raised
- How a patient should be managed if the FIT test level is not raised ("Safety Netting")
- What a GP should do if a patient does not return a FIT test after being asked to do it
- The accuracy of a FIT test in the detection of bowel tumours
- Ensuring equity and access to FIT testing
- Setting up a system for arranging FIT tests
- The areas where there is a lack of information and further research studies are needed

These guidelines were written by a group of specialists, GPs and patients brought together by the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG).

Common Questions That Patients Ask Regarding FIT Testing:

Why will my doctor ask me to do a FIT test?

FIT testing can help your doctor to assess you if you have bowel symptoms. The test can help your doctor to either reassure you or indicate that you need further tests.

How Do I Do a FIT Test?

The GP will arrange for a FIT testing kit to be sent to you, along with instructions on how to do the test. The kit includes a test stick which the patient inserts into their poo and a pot to place the stick in. This is then placed in a special envelope which is also provided and sent to be analysed. The GP or the local hospital will then inform the patient of the result.

What happens if the FIT Test Indicates that there is blood in my poo?

If the FIT test indicates that there is an increased level of blood in the poo then the GP will refer the patient to the local hospital for a further test, either a Camera test (Colonoscopy) or an 'X-ray' type of test called a CT scan to examine the bowel to see if there is a significant internal cause for the bowel symptoms.

What happens if the FIT Test indicates that there is no blood in my poo?

The majority of patients will not have a raised level of blood in the poo and the GP will be able to reassure these patients that it is very unlikely that there is a significant cause of their bowel symptoms. It is likely that their symptoms will settle down. The GP will advise the patient that if the symptoms do not settle after the FIT test then they should seek reassessment by their GP. In this situation, the GP may be able to reassure the patient but if there is ongoing concern, they may refer the patient for further assessment by a Specialist in the local hospital.