NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Quantitative faecal immunochemical tests to guide colorectal cancer pathway referral in primary care

Final scope

November 2022

1 Introduction

The medical technologies topic oversight group identified faecal immunochemical testing (FIT) as an adjunct to clinical assessment in guiding referral for people with high risk symptoms in primary care as suitable for guidance development by the Diagnostics Assessment Programme on the basis of a briefing note. The topic completed scoping in April 2020 but was paused due to changes in clinical pathways during the height of the COVID-19 pandemic. Following exceptional surveillance of suspected cancer: recognition and referral (NICE guideline NG12) and quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care (NICE diagnostics guidance 30), it was decided to resume the topic but rescope to take into account the changes to clinical practice. The revised scope was informed by discussions at the scoping workshop on 11 October 2022 and the assessment subgroup meeting on 2 November 2022.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and experts and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

Colorectal cancer may be associated with symptoms of rectal bleeding, a change in bowel habits, weight loss, anaemia, abdominal or rectal mass, abdominal pain and blood in stool (faeces). Several other conditions may present with blood in stools. However, the presence of small amounts of

hidden blood in stools (known as faecal occult blood) can indicate that there is bleeding from potentially malignant (cancerous) growths on the inner lining of the large intestine.

FIT is designed to detect small amounts of blood in a faecal sample by using antibodies specific to human haemoglobin. A positive FIT alone cannot confirm a diagnosis of colorectal cancer. Further assessment using colonoscopy or alternative testing by CT colonography is required to confirm diagnosis. FIT is being used in Bowel Cancer Screening for 2-yearly testing of asymptomatic men and women aged 60 to 74. People over the age of 74 years can contact the programme to request a screening kit. From 2021, the age range is being gradually reduced to start at the age of 50.

NICE's diagnostics guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care (DG30) recommends faecal occult blood testing in the low risk symptomatic population, that is people without rectal bleeding who present to primary care with unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer (NG12).

It has been suggested that FIT should be used for most people with suspected colorectal cancer who present to primary care regardless of risk based on symptoms. Clinicians have observed that many people on the suspected colorectal cancer referral pathway have no abnormal pathology found at colonoscopy. Therefore, triage with FIT could mean that people who are unlikely to have colorectal cancer may avoid colonoscopy, and those that are likely to have colorectal cancer can be prioritised more effectively (D'Souza et al. 2020) (see section 6.6). This may release colonoscopy capacity to allow people on non-urgent referral pathways to be seen more quickly.

2.2 Product properties

FIT is available as quantitative tests (using immunoturbidimetric or enzyme-linked immunosorbent assay [ELISA] methods to measure haemoglobin) and qualitative tests (using immunochromatographic test devices to detect haemoglobin). In line with DG30 this evaluation will focus on quantitative FIT.

Immunoturbidimetric FIT contains particles which are coated in antibodies specific to human haemoglobin. The antibodies bind to haemoglobin present in the faecal sample creating complexes which are detected using turbidimetry.

ELISA FIT uses antibodies specific to human haemoglobin to bind haemoglobin in the faecal sample to the surface of microtiter wells. This is then treated with chemicals to produce a colour change. The intensity of the colour is proportional to the amount of haemoglobin in the sample. Some assays may also include antibodies for human haptoglobin.

Different FIT may report outcomes using either the concentration of haemoglobin in the sampling device buffer (nanograms Hb/mL buffer) or as concentration of haemoglobin by mass of faeces (micrograms Hb/g faeces). As the amount and type of buffer used varies between manufacturers, the World Endoscopy Organization's expert working group on FIT for colorectal cancer screening recommended that micrograms Hb/g should be used as a standard measure that can be compared easily between tests (Fraser et al. 2015).

Table 1: Summary of interventions

Test (see sections 2.2.1 to 2.2.7 for more detail)	**Test principle**	**Sample size required** (mg)	**Measuring range** (micrograms Hb/g)	Limit of detection (micrograms Hb/g)	Limit of quantitation (micrograms Hb/g)	**Throughput**
HM-JACKarc	Immunoturbidimetry	2	7 to 400	0.6	1.25	200 samples per hour
FOB Gold	Immunoturbidimetry	10	Varies according to the analyser used	Varies according to the analyser used	Varies according to the analyser used	Dependent on the analyser used
OC-Sensor PLEDIA	Immunoturbidimetry	10	2 to 50,000	2	2	320 samples per hour
OC-Sensor iO	Immunoturbidimetry	10	2 to 200	2	4	88 samples per hour
NS Prime	Immunoturbidimetry	10	4 to 240	4	10	300 tests per hour
IDK TurbiFIT	Immunoturbidimetry	15	Varies according to the analyser used	Varies according to the analyser used	Varies according to the analyser used	Dependent on the analyser used
IDK Hemoglobin ELISA	ELISA	15	0.18 to 50	0.15	0.18	Dependent on the analyser used
IDK Hb/Hp complex ELISA	ELISA	15	0.25 to 50 micrograms HbHp/g	0.16 micrograms HbHp/g	0.25 micrograms HbHp/g	Dependent on the analyser used
QuikRead go iFOBT (point-of-care test)	Immunoturbidimetry	10	10 to 200	2.5	9.5	1 test at a time, measurement time is less than 2 minutes.

Information provided by companies or taken from the test's instructions for use document. ELISA, enzyme-linked immunosorbent assay; Hb, haemoglobin; Hp, haptoglobin. Accuracy should be analysed according to analyser used, if data is available.

2.2.1 HM-JACKarc system

The HM-JACKarc system (Hitachi Chemical Diagnostic Systems Ltd, Alpha Laboratories) is a fully automated quantitative immunoturbidimetric FIT system. The system comprises a sample collection device (designed to measure 2 mg of faeces) which contains 2 mL of stabilizing buffer, latex agglutination reagent, and buffer solution. The assay is compatible with the HM JACKarc analyser, which can process up to 200 samples per hour, with a maximum capacity of 80 samples per run.

2.2.2 FOB Gold

FOB Gold (Sentinel/Sysmex) is an automated quantitative immunoturbidimetric FIT system. It comprises faecal sample collection tubes (the SENTiFIT pierceTube faecal collection device) which collect 10 mg of faeces in 1.7 mL of buffer, and latex agglutination reagent. The FOB Gold kit is compatible with Sentinel's own SENTiFIT analyser as well as those manufactured by 5 other companies. The performance characteristics of the assay vary depending on which analyser is used. The throughput of the test is dependent upon the clinical chemistry analyser used to process the samples, but 270 samples can be run per hour on the SENTiFIT 270.

2.2.3 OC-Sensor

The OC-Sensor (Eiken Chemical/MAST Diagnostics) is a quantitative immunoturbidimetric FIT. It comprises faecal sample collection tubes, latex reagent and buffer. The OCAuto sampling bottles can hold 10 mg of faeces.

The test can be run on either the OC-Sensor PLEDIA or the OC-Sensor iO analyser, which differ in the number of samples they are able to process. The OC-Sensor PLEDIA can process up to 320 samples per hour, with a capacity of 200 samples per run. The OC-Sensor iO can process up to 88 samples per hour with a maximum capacity of 20 samples per run.

[redacted]

2.2.4 NS-Prime

The NS-Prime (Alfresa/Abbott) is an automated quantitative immunoturbidimetric FIT system. The NS-Prime comprises a specimen collection container which collects 10 mg of faeces in 1.9 mL of buffer solution

(Carroll et al. 2014). The test is run on the NS-Prime clinical chemistry analyser.

The NS-Prime haemoglobin reagent is specific to the NS-Prime analyser and cannot be used on other platforms. The NS-Prime analyser can run up to 220 samples at the same time, processing 300 tests per hour.

2.2.5 IDK TurbiFIT

The IDK TurbiFIT assay (Immundiagnostik) is an immunoturbidimetric FIT compatible with a range of automated clinical chemistry analysers from 16 manufacturers. The TurbiFIT kit comprises reagents, control samples, and calibration samples. IDK TurbiTUBE sample collection devices are available separately, which collect 15 mg of faeces in 1.5 mL of buffer. The performance characteristics and throughput of the assay vary depending on which analyser is used.

2.2.6 IDK Hemoglobin (human) and hemoglobin/haptoglobin complex ELISA tests

The IDK hemoglobin (human) ELISA (Immundiagnostik) is an immunoassay for the quantitative determination of human haemoglobin in faeces. It consists of:

- a microtiter plate, pre-coated in antibodies
- buffers for washing, extraction and sample dilution
- conjugate peroxidase-labelled antibodies
- standards and controls
- tetramethylbenzidine substrate (to induce the colour change)

The test requires an ELISA plate reader with a photometer (Dynex DS2 and DSX systems) to determine the result. The throughput of the test is dependent upon the clinical chemistry analyser used to process the samples.

The company also produce the IDK hemoglobin/haptoglobin complex ELISA, which is similar but uses anti-haptoglobin antibodies in the coated microtiter plate. The company recommends using this test in addition to a haemoglobin test to improve sensitivity for detection of bleeding adenomas or cancers of the upper intestine.

2.2.7 QuikRead go iFOBT

The QuikRead go (Aidian) is a point-of-care analyser that can be used for a number of different diagnostic tests, including the immunochemical faecal

occult blood test (iFOBT) which is an immunoturbidimetric test. The kits contain reagent capsules and buffer in prefilled cuvettes. Faecal sampling sets and control materials are supplied separately.

A single sample can be run at a time, and the test takes less than 2 minutes for the result to be displayed.

3 Target conditions

3.1 Colorectal cancer

Colorectal cancer is a form of cancer that starts in the colon and rectum. It is the fourth most common cancer in the UK with approximately 43,000 new cases and around 16,800 deaths per year (Cancer Research UK). Almost half of the people diagnosed with colorectal cancer in England and Wales survive at least 10 years after diagnosis. Early diagnosis is thought to improve survival. Risk factors for colorectal cancer include older age, dietary and lifestyle factors, genetics and family history of the disease (particularly conditions such as familial adenomatous polyposis or Lynch syndrome), having a history of previous cancer, having colorectal polyps, and having ulcerative colitis or Crohn's disease.

Diagnosis of colorectal cancer frequently requires more than 1 investigation. Diagnostic investigations involve an assessment of clinical symptoms in primary care followed by referral to a specialist for visual examination. Symptoms of colorectal cancer include rectal bleeding, a persistent change in bowel habits, persistent abdominal pain, persistent blood in stool, weight loss, anaemia and abdominal or rectal mass (see section 2.1). Although several conditions may be associated with the presence of human blood in stools, for example, haemorrhoids, hidden traces of blood in stools suggests early signs of colorectal cancer or pre-cancerous growths such as polyps.

3.2 Diagnostic care pathway

3.2.1 Referral on suspected cancer pathway

NICE's guideline on suspected cancer includes advice on assessing people presenting to primary care with certain clinical signs and symptoms that may be indicative of colorectal cancer. It makes the following recommendations:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if:

- they are aged 40 and over with unexplained weight loss and abdominal pain or
- they are aged 50 and over with unexplained rectal bleeding or
- they are aged 60 and over with:
  - iron-deficiency anaemia or
  - changes in their bowel habit, or
- tests show occult blood in their faeces (see section 3.2.2).

A suspected cancer referral (for an appointment within 2 weeks) should also be considered for:

- People with a rectal or abdominal mass
- Adults aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings:
  - Abdominal pain
  - Change in bowel habit
  - Weight loss
  - Iron-deficiency anaemia

A suspected cancer pathway referral means an urgent (2-week wait) referral directly by the GP after a clinical assessment of symptoms. The referral would be for the most appropriate test (for example, colonoscopy or CT colonography), or an urgent appointment with a specialist. These symptom-based criteria for referral have resulted in an increase in the number of referrals but there has not been a corresponding increase in the proportion of patients that are investigated who have cancer (Mozdiak et al. 2019). In addition, in 2020-21, a total of 377,163 people with suspected lower gastrointestinal cancer were seen under a suspected cancer pathway referral, of whom 88.9% were seen within 2 weeks (compared with an operational standard of 93%; NHS England 2021). Of 15,053 people treated for lower gastrointestinal cancer in 2020-21 under a suspected cancer pathway referral, only 50.6% received treatment within 62 days following an urgent GP referral (compared with an operational standard of 85%).

A negative FIT could potentially help to rule out suspected colorectal cancer and allow for alternative diagnostic testing. NICE's guideline on suspected cancer recommends safety netting for people with symptoms associated with an increased risk of cancer who do not meet the criteria for referral or other investigative action. Safety netting refers to processes used to avoid missing disease (cancer or otherwise) in people with negative test results (see section 6.4).

3.2.2 Testing for occult blood

NICE's diagnostic guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care recommends OC Sensor, HM-JACKarc and FOB Gold quantitative FIT to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer. People with positive test results (that is, a test result indicating the presence of occult blood in faeces, using a threshold of 10 micrograms of Hb/g of faeces) should be referred using a suspected cancer pathway for colorectal cancer.

In November 2020, NICE issued a speciality guide for patient management during the coronavirus pandemic on triaging patients with lower gastrointestinal symptoms, which was supported by the British Society of Gastroenterology (BSG). The advice was to continue to refer according to the NICE guideline on suspected cancer, but that the use of FIT could be used to help clinicians prioritise referrals. People with more than 100 micrograms Hb/g and no colonoscopy within the last 3 years would be referred for urgent endoscopy or CT. People with between 10 and 100 micrograms Hb/g, or people with more than 100 micrograms Hb/g who have had a colonoscopy requiring no further investigation in the last 3 years, would be referred for prioritised endoscopy or colonic imaging. People with less than 10 micrograms Hb/g would be managed using a safety netting process, which may include strategies for diagnosing other gastrointestinal conditions, and further monitoring for colorectal or other types of cancer (see section 6.4).

In 2022, the Association of Coloproctology of Great Britain & Ireland (ACPGBI) and the BSG published guidance on faecal immunochemical tests in patients with signs or symptoms of suspected colorectal cancer. It recommends that FIT should be used in primary care to prioritise people with clinical features of colorectal cancer for referral for urgent investigation, using a threshold of 10 micrograms Hb/g. However, it also recommends that people should not be excluded from referral from primary care on the basis of faecal immunochemical testing alone. Some people with less than 10 micrograms Hb/g may be managed in primary care provided appropriate safety netting is in place (see section 6.4). People with less than 10 micrograms Hb/g but with persistent and unexplained symptoms for whom the GP has ongoing clinical concern should be referred to secondary care for evaluation. This guidance was based on a systematic review of the available evidence, expert opinion and agreed by consensus. Economic evaluation was not conducted.

In October 2022, NHS England published a letter endorsing the use of the ACPGBI and BSG guidance on FIT in primary care. The letter also contains

recommendations on safety netting for people with negative FIT results (see section 6.4).

Scottish referral guidelines for suspected lower gastrointestinal cancer recommend using quantitative FIT, where available, for all people with persistent new colorectal non-urgent (see section 6.2) symptoms where referral to secondary care is being considered. A FIT result of more than 10 micrograms Hb/g is an indication for an urgent suspicion of cancer referral. The guideline notes that, if a person with high-risk symptoms is unable to complete, declines or is unlikely to return a test (see sections 3.3 and 7) then urgent referral is recommended.

Although a threshold of 10 micrograms Hb/g has been adopted by many centres to triage a symptomatic population, other thresholds may also be used (see section 6.1).

Clinical experts advised referral decisions should not be made using FIT results alone, and that symptoms and results from other tests (such as a full blood count) should also be considered. If people with symptoms do not return FIT kits (see section 3.3), referral should not be inappropriately delayed.

3.2.3 Diagnosis of colorectal cancer

Colonoscopy is often used for diagnosing colorectal cancer in people without major comorbidities. It can visualise the entire colon and biopsies can be taken and examined histologically to confirm a diagnosis, unless this is contraindicated (for example, in people who have recently had a heart attack). It is most frequently performed as an outpatient procedure. It requires adequate preparation of the colon using diet modification and laxative. Most people undergoing the procedure are offered sedation, painkillers or nitrous oxide gas. Clinical experts noted that colonoscopy is not a perfect test and can miss important signs of disease.

Because of its invasive nature and the risk of dehydration during colon preparation, colonoscopy may not be suitable for elderly people and those with comorbidities. For those people, CT colonography which is less invasive than conventional colonoscopy is an alternative imaging investigation of choice. ACPGBI/BSG guidance recommends that CT colonography is equivalent to colonoscopy for detection of colorectal cancer, and the choice should be determined by local expertise and availability.

Clinical experts advised that, for some people, other diagnostic techniques such as colon capsule endoscopy or flexible sigmoidoscopy may be

appropriate to investigate signs of potential colorectal cancer. Experts in secondary care said that, where available, FIT results are often used to inform the choice of further investigation based on capacity (see section 6.6).

3.2.4 Treatment of colorectal cancer

The most common finding during a colonoscopy is colorectal polyps, which can be removed using cauterisation or a snare. Some types of polyp (called adenomas) have a chance to become cancerous. If colorectal cancer is confirmed, NICE's guideline on colorectal cancer recommends further imaging tests, such as CT or MRI, to stage the cancer and determine what treatment is needed. Colonoscopy may also find other bowel diseases such as Crohn's disease, ulcerative colitis and diverticulosis, which may need further treatment and follow-up (see section 6.4). People with a positive FIT but no abnormalities detected during colonoscopy may be referred for further testing if a clinician thinks this is needed.

3.3 Patient issues and preferences

People presenting with symptoms, including abdominal pain, change in bowel habit, weight loss or anaemia may have varying severity of symptoms. False positive FIT results may cause anxiety and lead to unnecessary further investigations such as colonoscopy. Colonoscopy is an invasive procedure which is associated with various complications (including bleeding, infection, perforation of intestine) and very rarely death.

People with false negative results may be inappropriately reassured that they are not at risk of colorectal cancer and consequently they may ignore ongoing symptoms. On the other hand, there may be significant anxiety because of ongoing symptoms. False negative results could lead to delayed diagnosis which could have longer term consequences for that person.

Some people may not return FIT samples, either because they are unable to use the sample kits, or because they find the sampling process unacceptable (see section 7). ACPGBI/BSG guidance recommends that clinicians should follow-up with people with no FIT result to encourage them to return a sample or offer a replacement kit. Clinicians should inform people who decline to return a FIT test that their symptoms have not been fully investigated and encourage them to complete the test. Where no FIT result can be obtained, existing national or local guidelines should be used to assess the risk of colorectal cancer. Clinical experts advised that if people with symptoms do not return FIT samples, then referral should not be inappropriately delayed.

Some people may have received a negative FIT result from participating in the NHS bowel cancer screening programme. If subsequently presenting to primary care with symptoms suggestive of colorectal cancer, clinical experts advised that doing FIT would still be appropriate, as a much lower threshold would be used for a symptomatic population (see section 6.1). It is important to make sure that this distinction is clearly communicated to the person having the tests.

4 Comparator

Current practice is standard care according to current NICE guidelines (NG12 and DG30) which involves clinical assessment of symptoms by a GP in primary care. DG30 recommends that people with 'low risk' symptoms as described in NICE's diagnostic guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care would be triaged using FIT, while people with 'high risk' symptoms would be immediately referred on the suspected cancer pathway as described in section 3.2.1.

Feedback from clinical experts and stakeholders is that stratification by symptoms is a poor predictor of risk of colorectal cancer. Any resulting guidance that differentiates between the risk groups currently defined in NICE guidance would not address this problem. Therefore, despite the possibility of differential cost-effectiveness by subgroup, the intervention arm will not subgroup according to these risk categories to avoid making recommendations according to symptom-based criteria. The comparator is a blended group of people who would currently be considered under the guidance of NG12 and DG30. However, the comparator used in modelling may differ depending on the approach taken.

5 Scope of the assessment

Table 2 Scope of the assessment

Decision question	What is the most clinically and cost-effective way to use quantitative faecal immunochemical tests to reduce the number of people without significant bowel pathology who are referred to the suspected cancer pathway for colorectal cancer, taking into consideration potential colonoscopy capacity constraints for urgent and non-urgent referrals?
Populations	People presenting to primary care with gastrointestinal symptoms or signs indicating a risk of colorectal cancer (excluding people with rectal or anal mass, or anal ulceration – see section 6.2).

	Where evidence is available, subgroups may include: • Age • Sex • Ethnicity • People taking medications or with conditions which increase the risk of gastrointestinal bleeding • People with blood disorders that could affect the performance of the test (such as beta thalassaemia) • People with anaemia (including iron deficiency anaemia) Different threshold values may be needed for these subgroups. Although FIT is proposed to be offered to the population outlined above, it is possible that introduction of the test would have an indirect impact on people waiting for non-urgent referral to gastroenterology services and/or colonoscopy (see section 6.6).
Interventions	Quantitative FIT using specific thresholds of haemoglobin per g of faeces to guide referral. These tests could include: • HM-JACKarc • FOB Gold • OC-Sensor PLEDIA • OC-Sensor iO [redacted] • NS-Prime • IDK TurbiFIT • IDK Hemoglobin ELISA • IDK Hemoglobin/haptoglobin complex ELISA • QuikRead go iFOBT The testing strategies assessed (i.e. thresholds used) may depend on the availability of clinical effectiveness data.
Comparator	Current practice is standard care according to current NICE guidelines NG12 and DG30 (see section 4). This includes: • Clinical assessment and referral for further investigation in secondary care • Use of FIT (threshold of 10 micrograms Hb/g) to guide referral only for those with 'low risk' symptoms without rectal bleeding (in line with NICE guideline DG30).

	However, the comparator used in the model may differ depending on the approach taken.
Reference standard	The reference standards for assessing the accuracy of FIT are colonoscopy, CT colonography or long-term follow-up. Other reference standards will be considered where data using the preferred reference standard is unavailable.
Healthcare setting	Primary care
Outcomes: intermediate measures	Intermediate measures for consideration may include: • Diagnostic accuracy at different thresholds • Risk of colorectal cancer in relevant subgroups according to FIT threshold • Test failure rates • Prognostic implications of false negative results • Uptake of faecal immunochemical testing in primary care • Number/proportion of people referred to secondary care • Number/proportion of people followed up in primary care • Duration of validity of negative test (implications for follow-up) • Number/proportion of urgent specialist appointments • Number/proportion of urgent colonoscopies/CT colonography • Number/proportion of non-urgent colonoscopies/CT colonography • Time to colonoscopy/CT colonography • Time to diagnosis of colorectal cancer or other conditions • Number/proportion of colonoscopies/CT colonography that do not detect colorectal cancer • Number/proportion of colonoscopies/CT colonography that do not detect significant bowel pathology • Number/proportion of people presenting to emergency departments with symptoms of colorectal cancer
Outcomes: clinical	Clinical outcomes for consideration may include: • Number of colorectal cancer diagnoses • Number/proportion of colorectal cancer diagnoses from urgent referrals • Stage of detected cancers

	• Number/proportion of people identified with other bowel pathologies • Number/proportion of people with advanced adenomas detected or detected and treated • Morbidity including adverse events associated with colonoscopy • Mortality
Outcomes: patient-reported	Patient-reported outcomes for consideration may include: • Health related quality of life • Anxiety associated with waiting for referral or test results due to diagnostic delays, and further diagnostic workup • Preference for faecal testing versus colonoscopy
Outcomes: costs	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of equipment, reagents and consumables for FIT • Cost of staff and associated training • Medical costs of testing and care including further follow up and safety netting • Medical costs of adverse events from testing or further diagnostic work up, including those associated with false test results and inappropriate treatment.
Measuring cost-effectiveness	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

6.1 Thresholds for referral

NICE's diagnostic guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care recommends that results should be reported using a threshold of 10 micrograms Hb/g of faeces. The committee concluded that this threshold gave the test enough sensitivity to reliably rule out colorectal cancer in the low-risk population. Some experts advised that a lower threshold (for example, the limit of detection of the test) could be used to increase sensitivity and avoid missing cases of cancer. On the other hand, use of a higher threshold could reduce burden on colonoscopy services by increasing specificity, if the detection rate of colorectal cancer was not disproportionately compromised (by the associated reduction in sensitivity). Different thresholds may also be used for certain subgroups (for example, a lower threshold could be used if a person had iron-deficiency anaemia).

Two thresholds could be used to define low, intermediate and high risk populations. In this scenario, people in the intermediate risk group may have more intensive monitoring of their condition than in the low risk group, or be referred to a specialist safety netting pathway (see section 6.4).

The impact of using different thresholds, either to define 2 or 3 risk groups, should be investigated in the assessment.

6.2 Symptoms that are an indication for bypassing FIT

NICE's diagnostic guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care recommends FIT for people without rectal bleeding with unexplained symptoms. Clinical experts advised that rectal bleeding would no longer be considered a reason to bypass FIT. However, presence of a palpable rectal or anal mass, or anal ulceration may be reason to move straight to a 2-week wait referral bypassing FIT. Clinical experts said that FIT could still be useful alongside referral, to help choose the method of further investigation, and may be required by some secondary care centres.

6.3 Dual testing

Dual FIT (using 2 samples from different bowel movements rather than a single sample from 1 bowel movement) could be used to minimise the number of false negative results. However, this could increase the number of people who do not return samples and could also impact on laboratory capacity. This is a different scenario to using FIT as part of a safety netting programme (see section 6.4). Clinical experts agreed that people would be referred to the suspected cancer pathway if either FIT sample was positive. If possible, the impact of dual testing should be investigated in the assessment.

6.4 Safety netting and other conditions with gastrointestinal symptoms

The proposed approach of using FIT to triage people with gastrointestinal symptoms suggestive of colorectal cancer could result in many people with negative FIT results not being referred for further investigation with colonoscopy or CT colonography. However, these investigations can also be used to diagnose other conditions such as Crohn's disease, ulcerative colitis and diverticulosis, which may need further treatment and follow-up. In these situations, and cases with false negative results, use of FIT might introduce a delay to diagnosis.

Safety netting refers to processes used to avoid missing disease (cancer or otherwise) in people with negative test results. Clinical experts advised that

current safety netting practice is highly variable and is difficult to implement (see section 8).

NICE's guideline on suspected cancer recommends safety netting for people with symptoms associated with an increased risk of cancer who do not meet the criteria for referral or other investigative action. This may be planned within a timeframe agreed with the person, or initiated by the person if their symptoms recur, persist or worsen. The guideline also highlights the possibility of false negative results from FIT. ACPGBI/BSG guidance recommends that safety-netting protocols should include advice and strategies for the diagnosis of colorectal and extracolonic cancers, as well as other serious gastrointestinal conditions.

A letter published by NHS England recommends that safety netting could include:

- Providing clear information about who to contact if new symptoms develop or existing symptoms worsen
- Using e-referral systems to guide management of persistent or troublesome symptoms
- Offering a second FIT if ongoing clinical concerns remain
- Referral to a non-specific symptoms urgent cancer pathway
- Management in an outpatient setting following a non-urgent pathway.

The letter included an example of a non-urgent FIT-negative pathway from the North Central London Integrated Care Board. This pathway for people with persisting symptoms but a FIT result of below 10 micrograms Hb/g is based in secondary care and includes:

- Full blood count, repeat FIT, and virtual follow-up clinic within 8 to 10 weeks
- Consultant led virtual or telephone clinic to determine management plan
    - Discharge to primary care
    - Consultant upgrade to urgent cancer pathway
    - Further investigations on referral to treatment pathway.

Clinical experts said that such pathways are not widely available, and that safety netting is usually conducted in primary care and is patient-led (for example, if a person has new, persisting or worsening symptoms, they will get back in touch with their GP).

Safety netting should be incorporated into the assessment, examining the most likely implementation as well as exploring alternative scenarios such as FIT-negative clinics as part of sensitivity analyses.

6.5 Existing models

NICE's guideline on suspected cancer included an economic model which assessed the cost-effectiveness of diagnostic tests to diagnose colorectal cancer in patients aged 40 and over who presented in primary care with a change in bowel habit for the first time. The model combined a decision tree and Markov structure with states to capture the diagnosis and consequent staging of colorectal cancer. A lifetime horizon and a cycle length of 1 year were applied. The diagnostic tests modelled were guaiac faecal occult blood test, colonoscopy, CT colonography, barium enema and flexible sigmoidoscopy. The cost-effectiveness of FIT was explored in a scenario analysis based on a retrospective study reporting sensitivity of 74% and specificity of 86% for detecting colorectal cancer in symptomatic patients.

NICE's diagnostics guidance on faecal immunochemical tests in low-risk symptomatic patients assessed the cost-effectiveness of using faecal immunochemical tests to triage symptomatic people who are at low risk of colorectal cancer. FIT was compared with guaiac faecal occult blood testing and referral to colonoscopy without triage. The model was adapted from the model in NICE's suspected cancer guideline. The model consisted of 3 parts: a decision tree model reflecting the diagnosis of colorectal cancer, a Markov model to estimate long-term costs and effects (life years and QALYs) associated with the treatment and progression of colorectal cancer and a Markov model to estimate the life years and QALYs associated with those who do not have colorectal cancer.

The COLOFIT research project on FIT-based strategies for referral of people with suspected colorectal cancer consists of 4 work packages. These are a systematic review of evidence on FIT and risk factors for colorectal cancer; a mathematical model of risk for colorectal cancer; a survey on views on FIT from people with suspected colorectal cancer, healthcare professionals and other stakeholders; and a health economic model applying the results of the previous work packages to assess the use of FIT for people with possible colorectal cancer. The project is estimated to end in mid-2023.

6.6 Colonoscopy capacity and waiting times for suspected cancer pathway referrals

There are currently long waiting lists for colonoscopy (see sections 3.2.1 and 8). A letter published by NHS England states that, since the pandemic, waits

on the lower gastrointestinal pathway have lengthened more than for any other tumour group. In August 2022, 28% of people seen by a specialist for suspected colorectal cancer were not seen within 2 weeks of urgent referral, and 53% did not have a diagnosis within 28 days (NHS cancer waiting times, August 2022). Clinical experts also advised that waiting lists for non-urgent referrals to colonoscopy are currently much longer than the target 18 weeks. Introduction of FIT could help identify those people who are most likely to have colorectal cancer, and so help prioritise the waiting lists for further investigation.

Stakeholders highlighted that colonoscopy capacity is limited and therefore the Diagnostics Advisory Committee will need to consider real-world constraints during the decision-making process. The assessment should consider the constraints of current colonoscopy capacity and the impact of this on outcomes specified in the scope, including waiting times for both urgent and non-urgent referral to gastroenterology and colonoscopy services. Scenarios examining different capacity constraints could also be useful for committee decision making to inform future system needs.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Older people and Jewish people of central and eastern European family origin are thought to be at an increased risk of colorectal cancer. People with cancer are protected under the Equality Act 2010 from the point of diagnosis.

The tests may not be suitable for use in people with an existing diagnosis of inflammatory bowel disease and thalassaemia, some of whom may be covered by the disability provision of the Equality Act 2010. People with physical or cognitive disabilities may need support to obtain and submit a stool sample using the collection devices, or to understand the purpose of the test and the implications of the test results.

Cultural or demographic preferences may influence the acceptability of tests that require collection of a stool sample. Experience from the bowel cancer screening programme indicates that socioeconomic factors can also act as barriers to engaging with FIT programmes (Cancer Research UK).

Faecal haemoglobin concentrations may be greater in men than women and may also increase with age. Test cut-offs may therefore vary according to age and sex (Fraser et al. 2012).

Manufacturers suggest that samples for FIT should not be collected under certain circumstances, including diarrhoea, constipation, bleeding haemorrhoids, blood in the urine, when taking medications that increase the risk of bleeding, or when menstruating. This could result in a delay to diagnosis if people have to wait before obtaining a sample for FIT. Clinical experts advised that many of these circumstances relate to difficulty collecting samples or potential for contamination and are either outdated or overly cautious. They suggested that the decision to offer FIT should not be influenced by these factors.

8 Potential implementation issues

Potential implementation issues identified by the NICE adoption and impact team include:

Care pathway

- There is variation in practice for referral to colonoscopy.
  - Most high-risk people referred from primary care attend an urgent appointment in secondary care, where decisions on the next steps are made.
  - Some people go straight to colonoscopy following a telephone triage.
- The cancer diagnosis pathway will change with the development of Community Diagnostics Centres and the Faster Diagnosis Standard and this may have an impact on the use of FIT to guide referral to the cancer pathway.
- Ordering FIT in primary care and waiting for results may add a delay to the 2-week wait.
- Follow-up and monitoring of people with negative test results or who do not return tests (safety netting) is difficult to implement without clear systematic guidance and appropriate IT systems.

Colonoscopy capacity

- There are currently lengthy wait times for colonoscopy. Implementation of FIT has the potential to prioritise referrals for urgent colonoscopy, allowing those most in need to be seen more quickly.

Clinician confidence/acceptance

- There was concern that the risk of missing important pathology in this population may be higher than the low risk associated with colonoscopy.

Commissioning

- Increased funding will be required if quantitative FIT in primary care is to be extended to a high-risk population.
- Expanding the number of tests run by laboratories has potential to generate more money for the laboratory and allow the test to be run at a cheaper price. However, laboratories do not receive full reimbursement because payment goes to the laboratory through the trust.
- Some companies offer additional tests that can be done on the same faecal sample, for example tests for calprotectin.

Laboratory

- Reporting of FIT results may vary by laboratory.
- Different tests or analysers may report different absolute values for haemoglobin concentration from the same sample, which could impact on referral rates.

Connectivity

- New IT connectivity may be required between laboratories, GP practices and secondary care systems to have access to test results.

9 Authors

Tosin Oladapo
Topic Lead (until April 2020)

Jacob Grant
Topic Lead (from July 2022)

Frances Nixon
Technical Adviser (until July 2022)

Judith Shore
Technical Adviser (from July 2022)

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Appendix A Glossary of terms

Adenoma

A tumour or growth that is not cancerous (benign).

Colon capsule endoscopy

An investigation in which a person swallows a small capsule containing cameras. This takes pictures of the lining of the colon and communicates them wirelessly to a nearby receiver.

Colonoscopy

An investigation that allows doctors to examine the lining of the colon (large intestine) using a flexible tube that contains a camera and light source (colonoscope).

Computed tomography (CT) colonography

A test that uses CT scans to check the colon and rectum.

Faecal immunochemical test

A test which detects faecal occult blood using antibodies against human haemoglobin**.**

Flexible sigmoidoscopy

An investigation that allows doctors to examine the lining of the lower section of the colon (sigmoid) using a flexible tube that contains a camera and light source (sigmoidoscope).

Haemoglobin

A protein molecule found in red blood cells. Its presence in faecal samples indicates that gastrointestinal bleeding may be occurring.

Haptoglobin

Haptoglobin is a protein produced by the liver which binds to haemoglobin making it less likely to break down during transit through the gastrointestinal tract. The detection of haptoglobin is claimed to increase the likelihood of detecting lesions higher in the colon.

Limit of detection

The limit of detection of a test is the smallest amount of the substance being tested for that can be reliably distinguished from an absence of the substance.

Limit of quantitation

The limit of quantitation of a test is the amount of the substance being tested for below which the test cannot operate with acceptable precision.

Turbidimetry

An analytical technique in which the amount of light blocked by a sample is used to determine the concentration of a substance of interest.

Polyp

A small growth on the inner lining of the colon or rectum.

Appendix B Abbreviations

ACPGBI	Association of Coloproctology of Great Britain and Ireland
BSG	British Society of Gastroenterology
DG	Diagnostic guidance
ELISA	Enzyme-linked immunosorbent assay
FIT	faecal immunochemical test or testing
Hb	Haemoglobin
Hp	Haptoglobin
NG	NICE guideline

Appendix C References

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