NICE National Institute for Health and Care Excellence

NICE guidance

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

Diagnostics guidance
Published: 24 August 2023

www.nice.org.uk/guidance/dg56

Contents

This guidance replaces DG30.

This guidance partially replaces NG12.

This guidance is the basis of QS124.

1 Recommendations

1.1 Quantitative faecal immunochemical testing (FIT) using HM-JACKarc or OC-Sensor is recommended to guide referral for suspected colorectal cancer in adults:

- with an abdominal mass, or
- with a change in bowel habit, or
- with iron-deficiency anaemia, or
- aged 40 and over with unexplained weight loss and abdominal pain, or
- aged under 50 with rectal bleeding and either of the following unexplained symptoms:
  - abdominal pain
  - weight loss, or
- aged 50 and over with any of the following unexplained symptoms:
  - rectal bleeding
  - abdominal pain
  - weight loss, or

- aged 60 and over with anaemia even in the absence of iron deficiency.

  FIT should be offered even if the person has previously had a negative FIT result through the NHS bowel cancer screening programme. People with a rectal mass, an unexplained anal mass or unexplained anal ulceration do not need to be offered FIT before referral is considered.

1.2 Refer adults using a suspected cancer pathway referral (as outlined in NICE's guideline on suspected cancer) for colorectal cancer if they have a FIT result of at least 10 micrograms of haemoglobin per gram of faeces.

1.3 For people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces:

- safety netting processes should be in place
- referral to an appropriate secondary care pathway should not be delayed if there is strong clinical concern of cancer because of ongoing unexplained symptoms (for example, abdominal mass).

1.4 Clinicians should consider if people need additional help, information or support to return their sample.

1.5 Further research is recommended (see the section on further research) to:

- determine the clinical impact of using:
  - thresholds higher than 10 micrograms of haemoglobin per gram of faeces to guide referral
  - dual FIT
  - FIT in people aged under 40
- evaluate methods for improving access, uptake and return of FIT, especially in groups in which engagement is less likely
- determine how conditions or medicines that increase the risk of gastrointestinal bleeding affect the diagnostic accuracy of FIT.

1.6 Further research is recommended (see the section on further research) on the effectiveness of:

- FOB Gold
- IDK Hemoglobin ELISA
- IDK Hemoglobin/Haptoglobin Complex ELISA
- IDK TurbiFIT
- NS-Prime
- QuikRead go iFOBT.

Why the committee made these recommendations

FIT detects small amounts of blood in faeces, which is a sign of possible colorectal cancer. Evidence shows that offering the test in primary care can identify people who are most likely to have colorectal cancer. These people can then be prioritised for referral to secondary care, while people who are less likely to have colorectal cancer can avoid unnecessary investigations. This means that colonoscopy resources can be used for people who most need them.

There is clear evidence on the diagnostic accuracy of the HM-JACKarc and OC-Sensor tests. So, the HM-JACKarc and OC-Sensor tests are recommended. The evidence is less clear for other tests and the estimates of diagnostic accuracy are more uncertain, so further research is needed.

The economic model considers multiple testing strategies for referral across a range of thresholds. All testing strategies using HM-JACKarc or OC-Sensor are cost effective compared with the previous recommendations on testing and referral in NICE's guideline on suspected cancer (see section 2.3). This is because FIT allows available colonoscopy resource to be used more effectively.

The economic model suggests that using thresholds above 10 micrograms of haemoglobin per gram of faeces for referral is more cost effective than using lower thresholds. But this is uncertain because there is not enough evidence to support some of the assumptions about safety netting for these higher thresholds. There is also concern that using a higher threshold would reduce physician confidence in the test results (because more people

with cancer may be missed) and so affect clinical decision making. Further research is needed on how using higher thresholds would affect clinical outcomes and decision making.

There is a lack of evidence on using dual FIT in primary care, using FIT in people aged under 40, and using FIT in people who have conditions or medicines that increase the risk of gastrointestinal bleeding. So, further research is needed. Social research is also needed to find the best ways to improve access, uptake and return of FIT in groups that are less likely to return a faecal sample.

People with certain symptoms of colorectal or anal cancer (rectal mass, unexplained anal mass, or unexplained anal ulceration) do not need to be offered FIT before referral (see the recommendations on lower gastrointestinal tract cancers in NICE's guideline on suspected cancer). People who do not return faecal samples or who have a negative FIT result and ongoing unexplained symptoms may still need further investigation in secondary care. This may be through alternative referral pathways such as a non-specific symptoms pathway. It is important that GPs can refer people without a positive FIT result if they think it is necessary.

2 The diagnostic tests

Clinical need and practice

Hidden blood in faeces

2.1 Colorectal cancer may be associated with a variety of symptoms, including blood in faeces. Small amounts of hidden blood in faeces (known as faecal occult blood) can show that there is bleeding from the gastrointestinal tract, potentially from malignant (cancerous) growths on the inner lining of the large intestine. Several other conditions (such as inflammatory bowel disease) may also cause blood in faeces.

2.2 Faecal immunochemical testing (FIT) detects small amounts of blood in a faecal sample using antibodies specific to human haemoglobin. A positive FIT result alone cannot confirm a diagnosis of colorectal cancer. Further assessment using colonoscopy or CT colonography is needed to confirm diagnosis.

Care pathway and clinical need

2.3 Previously, NICE's guideline on suspected cancer recommended:

- offering FIT to adults presenting to primary care with 'low risk' symptoms of colorectal cancer, that is:
  - aged 50 and over with unexplained abdominal pain or weight loss
  - aged under 60 with changes in their bowel habit or iron-deficiency anaemia
  - aged 60 and over with anaemia even in the absence of iron deficiency

- using a suspected cancer pathway referral to immediately refer adults with 'high risk' symptoms, that is:
  - aged 40 and over with unexplained weight loss and abdominal pain
  - aged 50 and over with unexplained rectal bleeding
  - aged 60 and over with iron-deficiency anaemia or changes in their bowel habit
  - occult blood in their faeces shown by tests
- considering a suspected cancer pathway referral for adults:
  - with rectal or abdominal mass
  - 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.

2.4 People referred to secondary care typically have further investigation using colonoscopy, or sometimes CT colonography. Clinicians have observed that many people on the suspected colorectal cancer referral pathway do not have any unusual findings at colonoscopy. So, using FIT could mean that people who are unlikely to have colorectal cancer may avoid colonoscopy, and that people who are more likely to have colorectal cancer can be prioritised more effectively. Colonoscopy capacity is limited, and there are sometimes long waiting times. Using FIT could reduce the number of people referred for colonoscopy and so reduce the waiting times for people on non-urgent referral pathways.

2.5 In 2022, the Association of Coloproctology of Great Britain & Ireland (ACPGBI) and the British Society of Gastroenterology (BSG) guidance on FIT in patients with signs or symptoms of suspected colorectal cancer recommended using:

- FIT for most people presenting to primary care with clinical features of colorectal cancer to guide referral for urgent investigation
- a threshold of 10 micrograms of haemoglobin per gram of faeces.

The Scottish Government also made similar recommendations. The ACPGBI and BSG guidance was endorsed by NHS England and NHS Wales, and implementation has begun in some areas.

The intervention

2.6 The intervention in this assessment is quantitative FIT using specific thresholds of haemoglobin per gram of faeces to guide referral for people presenting to primary care with signs or symptoms suggestive of colorectal cancer.

2.7 The tests included in this assessment measure haemoglobin levels in faecal samples using either immunoturbidimetry or enzyme-linked immunosorbent assay (ELISA). Both methods use antibodies specific to human haemoglobin to bind to haemoglobin present in the faecal sample.

2.8 A summary of the technical specifications of the tests is presented in table 1. This information was provided by the companies or the tests' instructions for use. The limit of detection is the smallest amount of the substance being tested for that can be reliably distinguished from an absence of the substance. The limit of quantitation is the lowest amount of the substance being tested for that can be quantified with acceptable precision. See sections 2.9 to 2.17 for further details on the tests.

Table 1 Summary of test technical specifications

Test	Measuring range (micrograms of haemoglobin per gram of faeces)	Limit of detection (micrograms of haemoglobin per gram of faeces)	Limit of quantitation (micrograms of haemoglobin per gram of faeces)
FOB Gold	Analyser dependent	Analyser dependent	Analyser dependent
HM-JACKarc	7 to 400	2	7

Test	Measuring range (micrograms of haemoglobin per gram of faeces)	Limit of detection (micrograms of haemoglobin per gram of faeces)	Limit of quantitation (micrograms of haemoglobin per gram of faeces)
IDK Hemoglobin ELISA	0.18 to 50	0.15	0.18
IDK Hemoglobin/ Haptoglobin Complex ELISA	0.25 to 50 micrograms of haemoglobin–haptoglobin complex per gram of faeces	0.16 micrograms of haemoglobin–haptoglobin complex per gram of faeces	0.25 micrograms of haemoglobin–haptoglobin complex per gram of faeces
IDK TurbiFIT	Analyser dependent	Analyser dependent	Analyser dependent
NS-Prime	4 to 240	4	10
OC-Sensor iO	2 to 200	2	4
OC-Sensor PLEDIA	2 to 50,000	2	2
QuikRead go iFOBT	10 to 200	2.5	9.5

FOB Gold

2.9 FOB Gold (Sentinel/Sysmex) is an automated quantitative immunoturbidimetric FIT system. It comprises faecal sample collection tubes that collect 10 milligrams of faeces in 1.7 ml of buffer, and latex agglutination reagent. FOB Gold is compatible with Sentinel's own SENTiFIT series of analysers and analysers manufactured by 5 other companies. The performance characteristics of the assay and throughput of the test vary depending on which analyser is used. The SENTiFIT 270 can run 270 samples an hour.

HM-JACKarc

2.10 HM-JACKarc (Minaris Medical/Alpha Laboratories) is an automated quantitative immunoturbidimetric FIT system. It comprises a sample collection device, designed to measure 2 mg of faeces in 2 ml of buffer, latex agglutination reagent, and buffer solution. The assay is compatible with the HM-JACKarc analyser, which can process up to 200 samples an hour, with a maximum capacity of 80 samples per run.

IDK Hemoglobin ELISA and Hemoglobin/Haptoglobin Complex ELISA

2.11 The IDK Hemoglobin ELISA (Immundiagnostik) comprises:

- a microtiter plate, pre-coated with anti-haemoglobin antibodies
- buffers for washing, extraction and sample dilution
- conjugate peroxidase-labelled antibodies
- standards and controls
- tetramethylbenzidine substrate.

The test requires a 15 mg sample of faeces. It uses an ELISA plate reader with a photometer (Dynex DS2 and DSX systems) to determine the result. The throughput of the test depends on which system is used to analyse the samples.

2.12 The company also produces the IDK Hemoglobin/Haptoglobin Complex ELISA, which is similar but uses a microtiter plate pre-coated with anti-haptoglobin antibodies.

IDK TurbiFIT

2.13 IDK TurbiFIT (Immundiagnostik) is an immunoturbidimetric FIT assay compatible with a range of automated analysers from 16 manufacturers. The TurbiFIT kit comprises reagents, control samples and calibration samples. IDK TurbiTUBE sample collection devices are available separately and 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.

NS-Prime

2.14 NS-Prime (Alfresa/Abbott) is an automated quantitative immunoturbidimetric FIT system. It comprises a specimen collection container that collects 10 mg of faeces in 1.9 ml of buffer. The test is run on the NS-Prime 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 process 300 tests an hour with a maximum capacity of 220 samples per run.

OC-Sensor

2.15 OC-Sensor (Eiken Chemical/MAST Diagnostics) is a quantitative immunoturbidimetric FIT system. It comprises faecal sample collection tubes, latex agglutination reagent and buffer. The OC-Auto sampling bottles can hold 10 mg of faeces. The test can be run on either the OC-Sensor PLEDIA or OC-Sensor iO analysers, which differ in the number of samples they are able to process. Two other historical OC-Sensor devices (DIANA and MICRO) were also included in this assessment and assumed to be equivalent to the other OC-Sensor devices.

2.16 The OC-Sensor PLEDIA can process up to 320 samples an hour with a maximum capacity of 200 samples per run. The OC-Sensor iO can process up to 88 samples an hour with a maximum capacity of 20 samples per run. MAST Diagnostics states that the OC-Sensor iO will be replaced by the OC-Sensor CERES, which processes 90 samples an hour and has technical specifications equivalent to the OC-Sensor PLEDIA.

QuikRead go iFOBT

2.17 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 of 10 mg of faeces can be run at a time, and the result is displayed in less than 2 minutes.

The comparator

Standard care

2.18 The comparator is standard care according to previous NICE guidance. This begins with clinical assessment of symptoms by a GP in primary care. People with low-risk symptoms were triaged using FIT and people with high-risk symptoms were immediately referred using a suspected cancer pathway referral (see section 2.3).

Reference standards

2.19 The reference standards used for assessing the accuracy of FIT are colonoscopy, CT colonography or long-term follow up.

3 Committee discussion

The diagnostics advisory committee considered evidence on quantitative faecal immunochemical testing (FIT) to guide colorectal cancer pathway referral in primary care from several sources, including an external assessment report and an overview of that report. Full details are in the project documents for this guidance.

Attitudes towards FIT

3.1 Patient experts explained that people with symptoms suggestive of colorectal cancer have different attitudes towards specific ways of using FIT (such as choice of threshold). These depend on their personal approach to risk and there is no unified preference. The committee recognised that attitudes may be related to sociodemographic factors or disability (see section 3.7). It concluded that certain groups may need tailored resources or additional clinical or carer support to enable them to use FIT.

FIT in the screening programme

3.2 Patient and clinical experts commented that people and GPs often confuse FIT used in the NHS bowel cancer screening programme with FIT used in primary care for people with lower gastrointestinal symptoms. The committee emphasised that FIT should still be offered to people with symptoms suggestive of colorectal cancer even if they have previously had a negative FIT result through the screening programme. It is important to communicate that the thresholds are different and that the tests have different purposes in different populations.

Bypass symptoms

3.3 During consultation, stakeholders commented that some symptoms are currently considered 'bypass' or 'red flag' symptoms, meaning a referral should be made without waiting for a FIT result. The committee recalled that rectal or anal mass and anal ulceration were defined as bypass

symptoms in the assessment scope. Clinical experts commented that referral pathways including other bypass symptoms (such as iron-deficiency anaemia) may be overly cautious and would have been introduced when FIT was relatively new and less widely accepted. The committee noted that evidence on how iron-deficiency anaemia affects the performance of FIT is unclear (see section 3.7). It concluded that FIT was still appropriate for people with rectal bleeding or iron-deficiency anaemia. The committee agreed that a referral using a suspected cancer pathway referral was more likely for people with an abdominal mass. But, because this is not a specific symptom of colorectal cancer, a FIT result would still be useful to ensure that the person has the most appropriate investigation. So, the committee did not recommend abdominal mass as a bypass symptom but noted it as a possible reason to refer if the person does not return a sample or has a negative FIT result and there is strong clinical concern of cancer (see recommendation 1.3).

Clinical effectiveness

Populations included in the evidence base

3.4 Most of the evidence was from populations that did not exactly match the population defined in the assessment scope. Some populations only included people with high- or low-risk symptoms (see section 2.3), and some populations were unclear. The external assessment group (EAG) explained that sensitivity analyses indicated that these differences in study populations did not have a detectable effect on the estimates of diagnostic accuracy. But there was a large amount of variability between studies. Because some tests did not have evidence in the scope population, the EAG chose to include studies from a broader population. The committee concluded that the estimates of diagnostic accuracy based on this broad population were likely representative of the accuracy in the scope population.

Equivalence of different tests

3.5 The quantity and quality of the evidence base varied between tests. The committee noted recent evidence that different devices produce

different results from the same samples, and clinical experts stated that there is no universal reference standard for FIT. So, equivalence between devices could not be assumed. However, the committee noted that the available data was not clear enough for it to make evidence-based recommendations with different thresholds for different FIT devices. The committee concluded that methods for technical validation of FIT devices need to be improved to allow generation of comparative data without the need for large clinical trials.

Diagnostic accuracy of different tests

3.6 The committee noted that most studies used either HM-JACKarc (16 studies) or OC-Sensor (17 studies). For FOB Gold, 3 studies were initially identified, but these had a low number of participants. The combined estimates of accuracy from these studies were uncertain. The committee acknowledged that FOB Gold was previously recommended in NICE's diagnostics guidance 30 on quantitative FIT to guide referral for colorectal cancer in primary care, during the development of which the committee concluded that although there was less data for FOB Gold than for HM-JACKarc or OC-Sensor, it was likely to perform similarly in practice. However, in this assessment the committee observed that the evidence base for HM-JACKarc and OC-Sensor was now larger and the estimates of diagnostic accuracy were more certain than during the development of the previous diagnostics guidance. But the FOB Gold evidence base remained limited. During consultation, the manufacturer of FOB Gold submitted additional evidence, which reduced the uncertainty in the estimates of specificity. However, the committee felt that the uncertainty in the estimates of sensitivity was still too large, so the risk of missing cancers was too high. It concluded that more evidence was needed to reduce the uncertainty around the diagnostic accuracy of FOB Gold. Only 1 study was identified for each of IDK Hemoglobin ELISA, IDK Hemoglobin/Haptoglobin Complex ELISA, NS-Prime and QuikRead go iFOBT. No studies were found for IDK TurbiFIT. So, the committee recommended that HM-JACKarc and OC-Sensor could be used for FIT. It recommended further research on the clinical effectiveness (including diagnostic accuracy) of FOB Gold, IDK TurbiFIT, IDK Hemoglobin ELISA, IDK Hemoglobin/Haptoglobin Complex ELISA, NS-Prime and QuikRead go iFOBT.

Factors that could affect the performance of FIT

3.7 There was not enough evidence to make any alternative recommendations on how FIT should be used when there are factors that could affect test performance. During scoping, clinical experts suggested that factors such as age, sex, ethnicity, iron-deficiency anaemia, or medications or conditions that increase the risk of gastrointestinal bleeding could influence the threshold that should be used to guide referral, or affect the diagnostic accuracy of the test. Some people may also have difficulty providing samples because of cognitive or physical disability. The EAG found limited evidence in these subgroups and no conclusive evidence to determine whether FIT should be used differently in these groups. The EAG and committee members also noted that ethnicity and disability are generally poorly recorded in studies of FIT. Comments received during consultation suggested further research could be recommended for some subgroups. But the committee noted that evidence is already developing in this area, with algorithms such as COLOFIT that incorporate multiple factors alongside a FIT result. This should address some of these uncertainties and allow these factors to be considered alongside a FIT result. The committee recommended further research on the clinical utility of FIT in people aged under 40 and in people who have conditions or medicines that increase the risk of gastrointestinal bleeding because it felt that these were not already covered by ongoing studies.

Uptake of FIT

3.8 The committee reviewed evidence showing differences in the rate of return of FIT between sociodemographic groups based on age, sex, ethnicity and socioeconomic status. The EAG highlighted publications that proposed strategies to help encourage test return in these groups, such as following up after a sample is not returned, providing information in multiple languages, or providing counselling and education services. But it was not clear which methods would be the most effective, and different methods may be more appropriate for different groups. The committee also noted comments received during consultation that highlighted that people with physical disabilities such as visual impairment or reduced dexterity may have difficulties completing a FIT

kit. A patient expert highlighted that people who are neurodivergent or who have sensory issues may also have difficulty. Therefore, the committee recommended social research to determine the best way to improve access to and return of FIT, especially from groups in which engagement is less likely.

3.9 A patient expert suggested that healthcare professional involvement is important to drive engagement with testing. GP experts noted that the ability of primary care healthcare professionals to provide support is limited by workload and IT systems. They noted that support would be hardest to implement in the most underserved areas where engagement with testing is likely to be lower. Guidance or educational resources to help improve test uptake would be helpful to minimise geographical differences in care. Patient experts emphasised that information should be available in different formats and languages to maximise accessibility. The committee noted that NICE and associated stakeholders can support implementation of this guidance (see section 5).

Dual FIT

3.10 Dual FIT was considered as a testing strategy. The committee noted that the term 'dual FIT' is not well understood and can be interpreted in different ways. The committee clarified how it was referring to different testing strategies:

- Dual FIT uses 2 separate faecal samples collected from different bowel movements within a short time period. A positive result from either sample would indicate a referral to secondary care.
- Repeat FIT refers to using FIT in safety netting, when a second test is offered to people who have had a negative FIT result (see section 3.19).

3.11 The committee considered evidence from the EAG's clinical-effectiveness review that found that dual FIT generally improved sensitivity but decreased specificity compared with single FIT at the same threshold. Clinical experts noted that FIT results can vary between bowel movements because bleeding can be intermittent. So, using dual FIT could reduce the risk of missing people with cancer. The evidence on test uptake with dual FIT in primary care was less clear. The committee

noted that the evidence base for dual FIT was from secondary care and may not be generalisable to the primary care setting of this assessment because people may place more importance on a request from secondary care. The interval between the 2 samples also varied between studies, with some issuing the kits at the same time and others sending them separately. Therefore, the effect of asking for 2 samples on uptake in primary care was unclear. Patient experts said that confidence in FIT results may be higher with dual FIT. However, the committee recalled that certain groups may have difficulty with FIT kits or may be less likely to return a sample. It was concerned that asking for 2 samples could particularly affect these groups (see section 3.7) and may be difficult to implement, adding unnecessary complication or delay to the process. This could increase inequality in access to healthcare. The committee noted that the safety netting process is likely to include a repeat FIT for people with negative results (see section 3.19), so people may still do 2 tests when there is ongoing clinical concern. The committee recommended further research to evaluate the impact of using dual FIT on test uptake, decision making and clinical outcomes.

Inflammatory bowel disease

3.12 Several conditions other than colorectal cancer can cause gastrointestinal symptoms and blood in faeces, including inflammatory bowel disease (IBD; Crohn's disease or ulcerative colitis). IBD is also usually diagnosed in secondary care through investigations such as colonoscopy. The EAG's clinical review found that the estimates of the diagnostic accuracy of FIT for IBD were more uncertain than those for colorectal cancer, and the sensitivity was generally lower. However, clinical experts did not think that introducing FIT would have a substantial effect on people who have IBD because GPs are likely to order a calprotectin test at the same time as FIT, which is a more accurate test for IBD (see NICE's diagnostics guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel). The committee reiterated that the focus of this assessment was using FIT to guide referral pathways for colorectal cancer, and that FIT is not intended to replace investigations for other conditions. It highlighted existing guidance that can be followed to ensure people with IBD and other non-cancer conditions do not experience delays to diagnosis, such

as the British Society of Gastroenterology (BSG) guidelines on the investigation of chronic diarrhoea or management of inflammatory bowel disease.

Cost effectiveness

Cost effectiveness of FIT

3.13 The committee agreed that using FIT for people with signs or symptoms suggestive of colorectal cancer was likely to be cost effective compared with using FIT as outlined in previous NICE guidance (see section 2.3). People with a rectal mass, an unexplained anal mass or unexplained anal ulceration do not need a FIT test before referral, as outlined in the recommendations on lower gastrointestinal tract cancers in NICE's guideline on suspected cancer. The economic model estimated that all testing strategies using HM-JACKarc or OC-Sensor were cost effective. This was because costs were saved by reducing the overall number of colonoscopies, but there was also a very small loss of health resulting from people who had false negatives from their FIT test. The EAG stated that the quality-adjusted life year (QALY) loss was equivalent to less than 1 day of full health for all people in the cohort. The committee noted that the model predicted that reducing the number of colonoscopy referrals would likely reduce secondary care waiting times for most people. However, the average time to diagnosis was increased overall because some people with false-negative FIT results would have very long waiting times.

Assumptions in the economic model

3.14 The committee agreed that the overall conclusions of the economic model were reasonable. However, there was uncertainty in specific cost-effectiveness estimates because many inputs were based on clinical expert opinion when evidence was not available. Some committee members thought that the times to diagnosis used in the base case were pessimistic. But a scenario analysis that used shorter times to diagnosis resulted in a more favourable cost-effectiveness estimate for FIT than in the base case. Primary care experts thought that the number of

additional GP appointments for people in primary care was too low, but not so low that the overall conclusion of cost effectiveness would be changed. The proportion of people who would be referred to secondary care despite a negative FIT result was based on clinical experts' experience with existing guidance (see section 2.5) and NICE's diagnostics guidance 30, which recommended a threshold of 10 micrograms of haemoglobin per gram of faeces. Clinical experts thought that using a higher threshold would reduce physician confidence in the test. As a result, the proportion of people being referred without a positive FIT result would be higher than modelled. Therefore, the cost-effectiveness results at higher thresholds were more uncertain.

Testing strategies

3.15 The committee decided that testing a single faecal sample and using a single threshold to inform referral decisions was the best strategy. It noted that the economic model predicted that using dual FIT would be slightly less cost effective than single FIT but would also reduce the QALY loss from false negatives. However, it recalled that dual FIT could disadvantage groups that are less likely to return samples and introduce additional implementation issues (see section 3.7 and section 3.11). The committee concluded that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity.

3.16 The committee noted that using 2 thresholds to define low-, intermediate- and high-risk groups appeared slightly less cost effective than using 1 threshold. Clinical experts also advised that using 2 thresholds would complicate referral decisions and make it harder to understand what the results mean in practice, which may reduce cost effectiveness more than predicted by the model.

Choice of threshold

3.17 The committee concluded that a threshold of 10 micrograms of haemoglobin per gram of faeces should be used to guide referral decisions. It acknowledged that the economic model suggested a threshold of 100 micrograms of haemoglobin per gram of faeces would be most cost effective. However, the committee recalled that the cost-

effectiveness estimates at higher thresholds were more uncertain (see section 3.14). Thresholds below 10 micrograms of haemoglobin per gram of faeces were not considered. This was because they were less cost effective and approached the limits of quantitation for many of the tests, which may reduce the reliability of results (see section 2.8).

3.18 Economic experts highlighted that cost-effectiveness estimates improved the most between lower thresholds. They suggested that moving to a threshold of 20 micrograms of haemoglobin per gram of faeces could produce a gain in cost effectiveness without losing physician confidence. Clinical experts disagreed that physicians would accept a higher threshold because of the risk of false-negative results but conceded that there was no evidence on how the choice of threshold affects decision making. So, the committee recommended further research on the clinical impact of using different thresholds to guide referral to understand if referrals would decrease by a similar proportion as predicted by the model.

Implementation of safety netting

3.19 The committee discussed safety netting for people who do not return a test or people with negative FIT results who have ongoing unexplained symptoms. It commented that no evidence was presented on the relative effectiveness of different safety netting approaches, but possible options had been explored in the economic model. The committee stated that clear guidance will be needed to ensure that safety netting is implemented consistently and effectively. It noted that advice is available in:

- the section on safety netting in NICE's guideline on suspected cancer
- the Association of Coloproctology of Great Britain & Ireland (ACPGBI) and BSG guidance on FIT in patients with signs or symptoms of suspected colorectal cancer

- the 2022 NHS England letter endorsing FIT.

  Clinical experts highlighted that the exact approach of available safety netting is likely to differ across the UK. The implementation of safety netting used in the model for people with negative FIT results or who did not return a test was based on clinical advice. Options included:

- referral to secondary care because of ongoing clinical concern, either through suspected cancer or non-urgent pathways
- management in primary care ('watch and wait')
- offering another FIT test (see the section on dual FIT).

3.20 Clinical experts emphasised that having a positive FIT result should not be an absolute requirement for referral to secondary care. This is because it is possible to have a false-negative result and some people may not be able to complete a test, either because of physical or cognitive disability or because of barriers to test uptake. So, the option to refer should always be available if GPs think it is needed, and secondary care centres should be able to accept referrals without a positive FIT result. Clinical experts highlighted that a non-specific symptoms pathway may be more appropriate than a colorectal cancer pathway for some people.

4 Recommendations for further research

4.1 Further research is recommended on how using thresholds higher than 10 micrograms of haemoglobin per gram of faeces to guide referral affects decision making and clinical outcomes.

4.2 Further research is recommended on how using dual faecal immunochemical testing (FIT) in primary care (see section 3.10) affects test access, uptake and clinical decision making.

4.3 Further research is recommended on the diagnostic accuracy of FIT in people aged under 40 because they may be less likely to have colorectal cancer but more likely to have other bowel conditions such as inflammatory bowel disease (IBD).

4.4 Social research is recommended to evaluate methods to improve access, uptake and return of FIT, especially in groups in which engagement is less likely, such as:

- men
- people from ethnic minority backgrounds
- people aged under 40
- people with lower socioeconomic status
- people with physical disabilities, including visual impairment and reduced dexterity
- people with cognitive disabilities or mental health conditions
- neurodivergent people.

4.5 Further research is recommended to determine how conditions (such as IBD) or medicines (such as aspirin) that may increase the risk of gastrointestinal bleeding affect the diagnostic accuracy of FIT.

4.6 Further research is recommended to assess the effectiveness (including

diagnostic accuracy, failure rate and test uptake) of:

- FOB Gold
- IDK Hemoglobin ELISA
- IDK Hemoglobin/Haptoglobin Complex ELISA
- IDK TurbiFIT
- NS-Prime
- QuikRead go iFOBT.

5 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition, NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 4 into its guidance research recommendations database and highlight these recommendations to public research bodies.

6 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Caroline Addison
Consultant clinical scientist, Queen Elizabeth's Hospital, Gateshead

Mary Craig
Macmillan GP cancer lead, Aneurin Bevan University Health Board

Farhat Din
Professor and honorary consultant colorectal surgeon, University of Edinburgh and Western General Hospital

Michael Gray
Specialist lay committee member

John Morris
Specialist lay committee member

Brian Nicholson
GP and clinical lecturer, University of Oxford

Edward Seward
Consultant gastroenterologist, University College London Hospitals

Baljit Singh
Consultant colorectal surgeon and honorary associate professor, University Hospitals Leicester

James Stephenson
Consultant gastrointestinal and abdominal radiologist, University Hospitals Leicester

NICE project team

Each diagnostics evaluation is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Jacob Grant
Topic lead

Judith Shore
Technical adviser

Toni Gasse
Project manager

ISBN: 978-1-4731-5356-1

Accreditation