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Diagnostics Advisory Committee

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

The following documents are made available to stakeholders:

1. **Stakeholder comments on the Diagnostic Consultation Document and responses**

2. **Addendum number 3: to the External Assessment Report**
   prepared by the External Assessment Group, School of Health and Related Research (ScHARR), The University of Sheffield.

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NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Draft guidance – Themed comments

Diagnostics Advisory Committee date: 27 July 2023

THEME: Bypass symptoms

Comment number	Name and organisation	Section number	Comment	NICE Response
1	Web comment (organisation not stated)	1.1	Locally we also exclude anal mass and anal ulceration and the result of FIT is not required for abdo mass or IDA but FIT does need to be requested	Thank you for your comment. People with anal mass and anal ulceration are not included in the population for this assessment as they are already covered by the recommendation in NICE's guideline on suspected cancer (NG12) on anal cancer. Further clarification has been added to the rationale and sections 1.1 and 3.3 of the guidance.
8 part 2	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	1.3	For Lancashire & South Cumbria Cancer Alliance we define 'red flag symptoms' as IDA, rectal/abdo palpable mass/rectal bleeding. In these cases FIT results should not be waited for before referral.	Thank you for your comment. During scoping it was established that rectal and anal mass or anal ulceration would be considered bypass symptoms, and so these are not included in the population eligible for FIT. This has been clarified in recommendation 1.1. People with anal mass and anal ulceration are already covered by the recommendation in NICE's guideline on suspected cancer (NG12) on anal cancer. The committee agreed that FIT was still appropriate for people with rectal bleeding or iron-deficiency anaemia (see committee considerations in sections 3.3 and 3.7 of the guidance). The committee felt that people with abdominal mass should be referred but a FIT result is still useful to guide investigation in secondary care. So, abdominal mass is included in the population but is referred to in recommendation 1.3 as an example of a symptom that may be a reason to refer in people who have

Comment number	Name and organisation	Section number	Comment	NICE Response
				not returned a sample or who have a result less than 10 micrograms per gram.
76 part 2	Web comment Cancer Research UK	1.1	The guideline could be clearer on the appropriate management of patients with a rectal mass i.e., that they should be referred on without requesting a FIT first. Additionally, including abdominal mass as an exemption would be welcomed, alongside a recommendation to request a FIT alongside a referral of patients with abdominal mass, as per BSG, Scottish and Welsh guidance.	Thank you for your comment. People with rectal mass are not included in the population for this assessment, as it was established during scoping that rectal mass would be considered a bypass symptom. This has been clarified in the rationale and in sections 1.1 and 3.3 of the guidance. NICE's guideline on suspected cancer (NG12) also provides guidance on referral for people with rectal mass. The committee felt that people with abdominal mass should be referred but a FIT result is still useful to guide investigation in secondary care. So, abdominal mass is included in the population but is referred to in recommendation 1.3 as an example of a symptom that may be a reason to refer in people who have not returned a sample or who have a result less than 10 micrograms per gram.
100 part 3	NHSE		3. We recommend that NICE aligns with BSG for abdominal masses and suggest the following 'patients with signs of an abdominal mass should be referred urgently, however a FIT should be requested simultaneously in primary care to inform the subsequent investigation'.	Thank you for your comment. The committee felt that people with abdominal mass should be referred but a FIT result is still useful to guide investigation in secondary care. So, abdominal mass is included in the population but is referred to in recommendation 1.3 as an example of a symptom that may be a reason to refer in people who have not returned a sample or who have a result less than 10 micrograms per gram.

THEME: Dual FIT

Comment number	Name and organisation	Section number	Comment	NICE Response
11	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	3.7	This 'testing strategy' has been commissioned for years in Lancashire & South Cumbria. 2 FIT tests are completed 24 hours apart and the subsequent study on our own data (30,000+ records), revealed that where there were 2 negative FIT tests in primary care the pt had a lower than population average of having colorectal cancer (0.04%). 'A cohort study of duplicate faecal immunochemical testing in patients at risk of colorectal cancer from North-West England': https://bmjopen.bmj.com/content/12/4/e059940 I would like to see this study referenced if possible.	Thank you for your comment. The study referenced is included in the external assessment report in the section that reviews dual FIT data (section 4.3.7). It has therefore formed part of the evidence base presented to the committee. The committee noted that the evidence base for dual FIT was from secondary care, so may not be generalisable to the primary care setting of this assessment because people may place more importance on a request from secondary care – please see section 3.11 in the guidance for more detail.
12	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	3.11	I'm unsure of the rationale that a pt who doesn't want to return one kit would be more put off when requested to send 2 FIT kits to their GP? We have not found this in LSCCA. Surely if a pt doesn't like the idea or are unable of completing 2 FIT kits, they would feel the same about 1..? Section 1.4 talks of the safety netting procedures in primary care to ensure a pt is supported to return their sample; would this not suffice as a safety net for these patients?	Thank you for your comment. The committee felt that asking for 2 kits could add unnecessary complication or delay to the process. It noted that the evidence on uptake for dual FIT is from secondary care, which 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 external assessment group noted that the Hunt study cited in comment 11 did not provide the number of people who were asked to complete a FIT but did not return a sample. Further research was therefore recommended on how using dual FIT in primary care affects test access, uptake and clinical decision making. Please see sections 3.11 and 4.2 in the guidance for more detail.
33 part 2	Web comment (organisation not stated)		I have commented below that a dual FIT offers significant benefits and safety netting and a double negative FIT with normal haemoglobin has such a high NPV for CRC that referral is unnecessary, reducing the pressure on endoscopy. I do not think that a two FIT approach could create inequality in access. Indeed i would suggest that a single FIT approach could create inequality in diagnosis. I would suggest that	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity, so more people would be referred than

Comment number	Name and organisation	Section number	Comment	NICE Response
			NICE recommend central funding for decision diagnostics such as FIT; the evidence fro use is overwhelming and we must not allow local financial barriers stopping the access to this test	if single FIT is used. It concluded that the potential drawbacks of dual FIT might outweigh the benefits of increased sensitivity. Further research was therefore recommended on how using dual FIT in primary care affects test access, uptake and clinical decision making. Please see sections 3.15 and 4.2 in the guidance for more detail. Recommendations on sources of funding are outside the remit of NICE guidance.
36	Web comment (organisation not stated)	1.4 Safety netting processes should be in place for people:	safety netting should include a dual FIT approach- more comments later	Thank you for your comment. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results – please see sections 3.11 and 3.19 in the guidance.
38	Web comment (organisation not stated)	1.7 The economic model also considers a testing strategy using 2 faecal samples, but evidence suggests that certain groups are less likely to return any samples. So, asking for 2 samples for FIT could create inequality in access.	Is there evidence that certain groups are less likely to return any samples or is this opinion? Even if there is evidence of this for a single FIT, it cannot be used as evidence that a two FIT approach could create inequality in access. Surely the "inequality" argument applies more to the single test, and therefore cannot be used to dismiss 2 FIT tests. I would argue that there is no evidence that 2 FIT testing could create inequality in access, and this opinion could have detrimental effects. Evidence shows that a two FIT approach increases sensitivity, increases specificity and the NPV of two negative FITs with normal haemoglobin allows fro reduced referral. Thus it could be argued that a single FIT approach will create inequality in access to further diagnostics	Thank you for your comment. The committee reviewed evidence showing differences in the rate of return of FIT between sociodemographic groups based on age, sex, ethnicity and socioeconomic status. This is detailed in section 4.3.14.4 of the external assessment report. The committee felt that asking for 2 kits could add unnecessary complication or delay to the process, and may particularly affect members of these groups. It concluded that the potential drawbacks of dual FIT might outweigh the benefits of increased sensitivity. The external assessment group commented that it did not identify any studies that demonstrated that specificity was increased by use of dual FIT when interpreting “either test positive” as a positive test, and when comparing results for dual FIT to single FIT at the same threshold in the same study. Further research was therefore recommended on how using dual FIT in primary care affects test access, uptake and clinical decision making. Please see sections 3.8, 3.11, 3.15 and 4.2 in the guidance for more detail.

Comment number	Name and organisation	Section number	Comment	NICE Response
41	Web comment (organisation not stated)	3.7 Experts also highlighted that there could be additional implementation issues if twice as many sample kits were needed, such as increased reliance on mail services or GP capacity.	this statement is unclear. are the experts suggesting that a two FIT approach would put excessive pressure on the mail service? I provide a 2 FIT service and both collecting devices are issued to the patient at the same time, so no increased pressure on GPs	Thank you for your comment. The committee acknowledged comments from centres where dual FIT is in use. It noted that when 2 sample kits are given at the same time the pressure on the mail service or GPs would not increase. This sentence has been removed from the guidance. Please see section 3.11 for more detail.
42	Web comment (organisation not stated)	3.7 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.	i would question the evidence that dual FIT decreased sensitivity. Hunt et at https://bmjopen.bmj.com/content/12/4/e059940 showed that a two FIT approach improved specificity (I am a co-author) A cohort study of duplicate faecal immunochemical testing in patients at risk of colorectal cancer from North-West England Hunt N, et al. BMJ Open 2022;12:e059940. doi:10.1136/bmjopen-2021-059940	Thank you for your comment. Dual FIT was not stated to reduce sensitivity. The external assessment group included the Hunt study in their report, but were not able to find any data in it relating to specificity for single and dual FIT to enable a comparison of the effect on specificity, and no conclusion about specificity appears to have been drawn by the authors.
43	Web comment (organisation not stated)	3.7 However, the committee recalled that certain groups are less likely to return a sample. It was concerned that asking for 2 samples could particularly affect	again, i would challenge this assertion. In our paper (quoted above) we found that 95% patients (n=28 622) completed two FIT samples. Thus "concern" that asking fro 2 FITs "could increase inequality in access to healthcare" is unevidenced. If people do "none" then that is a concern for all strategies; even if some patients do one and not two, then that should not be a basis of rejecting two based on inequality, as one would still be received	Thank you for your comment. The external assessment group commented that the study cited did not provide the number of people who were asked to complete a FIT but did not return a sample. Additionally, the committee noted that the evidence on uptake for dual FIT is from secondary care, which may not be generalisable to the primary care setting of this assessment because

Comment number	Name and organisation	Section number	Comment	NICE Response
		these groups (see section 3.5). This could increase inequality in access to healthcare.		people may place more importance on a request from secondary care. Further research was therefore recommended on how using dual FIT in primary care affects test access, uptake and clinical decision making. Please see sections 3.11 and 4.2 in the guidance for more detail.
44	Web comment (organisation not stated)	3.11 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	Again i would challenge this. I accept that a dual test would cost more but the sensitivity and specificity would improve. In addition the NPV of two negative FITs (with no evidence of anaemia) is over 99% giving primary care assurance that referral and colonoscopy/2w referral is not needed. a dual approach is not complicated! if two NEG then high probability that CRC not present, if EITHER is POS then referral is required in a low risk symptomatic patient	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity, so more people would be referred than if single FIT is used. The external assessment group commented that it did not identify any studies that demonstrated that specificity was increased by use of dual FIT when interpreting “either test positive” as a positive test, and when comparing results for dual FIT to single FIT at the same threshold in the same study. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern.

Comment number	Name and organisation	Section number	Comment	NICE Response
		implementation issues (see section 3.5 and section 3.7). The committee concluded that drawbacks of dual FIT were likely to outweigh the potential benefits of increased sensitivity. The committee noted that using 2 thresholds 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.		
52	Bowel Cancer UK	6.3	Dual testing On dual testing, the project run by scientists at the University of Edinburgh and the data it produced, illustrated that dual testing can improve accuracy and should be	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased

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			considered. Two groups of NHS Lothian patients who had been referred urgently to the Edinburgh Colorectal Surgery Unit were used to compare the use of a single FIT and dual testing. 'They found that doing two FIT tests detected 96.6 per cent of bowel cancer cases correctly, whereas undertaking just one test only detected 84.1 per cent. The median time between the two tests was 13 days. The study also showed that 16.8 per cent of those to complete two tests had sufficient variation in their test results to change their management plan. This occurred irrespective of significant bowel conditions and highlights the benefit of repeated testing, experts say' (University of Edinburgh, May 2023). The Scottish colorectal cancer referral pathway already incorporates dual testing and data from this programme suggests that 'requesting a second FIT, in patients where the first f-Hb was < 10ugHb/g faeces, increases the FIT sensitivity from 84 to 97%.' It does, however, highlight that dual testing will 'also increase colonoscopy demand by up to 9.7% unless applied only in patients with persistent symptoms and ongoing clinical concern' (Scottish Government, Quantitative Faecal Immunochemical Test (qFIT) for Patients with Colorectal Symptoms Guidance for Primary Care, May 2022). Given the results of the study produced by the University of Edinburgh and data from the Scottish colorectal cancer referral pathway, we believe further investigation of dual testing is warranted and should be considered as part of this assessment.	specificity. So, using dual FIT could reduce the risk of missing people with cancer. But, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. It concluded that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern.
56	Web comment (organisation not stated)	1.7 The economic model also considers a testing strategy using 2 faecal samples, but evidence suggests that certain groups are less likely to return any samples. So, asking for 2 samples for FIT could create	Evidence (Hunt et al,2021) indicates that two FIT having a significantly higher negative predictive value than a single FIT. While certain groups may be less likely to return samples, given the benefits of using two for the patients that do return it, it seems counter-intuitive not to recommend use of two FITs. Perhaps use of two could be recommended so long as appropriate support/safety netting is in place to reduce inequality in access.	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity. So, using dual FIT could reduce the risk of missing people with cancer. But, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. It also noted that the economic model predicted that using dual FIT would be slightly less cost effective than single FIT. It concluded that the potential drawbacks of dual FIT were likely to outweigh the

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		inequality in access.		benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern. Please see section 3.11, 3.15 and 4.2 for more detail.
57	Web comment (organisation not stated)	1.7 Social research is needed to find the best ways to improve uptake and return of FIT in groups that are less likely to return a faecal sample.	This ties into the above paragraph. Certain groups are less likely to return a FIT, regardless of whether one or two are requested. It seems counter-intuitive not to recommend use of two FITs, where appropriate work has been undertaken to minimise inequality in access.	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity. So, using dual FIT could reduce the risk of missing people with cancer. But, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. It also noted that the economic model predicted that using dual FIT would be slightly less cost effective than single FIT. It concluded that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern. Please see section 3.11, 3.15 and 4.2 for more detail.

Comment number	Name and organisation	Section number	Comment	NICE Response
59	Web comment (organisation not stated)	3.7 However, the committee recalled that certain groups are less likely to return a sample. It was concerned that asking for 2 samples could particularly affect these groups (see section 3.5). This could increase inequality in access to healthcare. Experts also highlighted that there could be additional implementation issues if twice as many sample kits were needed, such as increased reliance on mail services or GP capacity	Certain populations are less likely to return kits, regardless of whether one or two are requested. If the appropriate support/research is available/undertaken to reduce inequality in access and encourage return of the kits, it seems that those patients who do return kits are being disadvantaged. Completing two kits significantly reduces the risk of missing a colorectal cancer (Hunt et al, 2021) and reduces the risk of patients not being referred on a secondary care pathways due to false negatives. For areas that have already implemented two FITs, this is working extremely well. Use of two could be recommended where risks/barriers are mitigated.	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity. So, using dual FIT could reduce the risk of missing people with cancer. But, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. It also noted that the economic model predicted that using dual FIT would be slightly less cost effective than single FIT. It concluded that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern. Please see section 3.11, 3.15 and 4.2 for more detail.
60	Web comment (organisation not stated)	3.13 because of the risk of false negative results	Use of two FITs could help reduce this risk	Thank you for your comment. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity. So, using dual FIT could reduce the risk of missing people with cancer. But, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that

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				are already less likely to return samples and introduce additional implementation issues. It also noted that the economic model predicted that using dual FIT would be slightly less cost effective than single FIT. It concluded that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. The committee noted that a second FIT is likely to form part of the safety netting process (repeat FIT) for people with negative results, so people may still get 2 FITs where there is ongoing clinical concern. Please see section 3.11, 3.15 and 4.2 for more detail.
61	Web comment (organisation not stated)	3.14 offering another FIT test	Use of two FITs initially would be very similar to this but safety nets the patient sooner. While there may be patients that won't return two FITs, there may also be patients that will not re-present to their GP with ongoing symptoms and may not be safety netted. Two FITs completed initially would have reduced the risk of a false negative in the first instance.	Thank you for your comment. Recommendation 4.4 was expanded to evaluate methods to improve access to FIT in the identified groups, in order to address differences in factors such as whether or not a person contacts their GP when they have symptoms.
62	Web comment (organisation not stated)	3.15 So, the option to refer should always be available should GPs think it is needed	Using two FITs reduces the risk of false negatives. There should be clearer guidance on when a GP can refer with a negative FIT (e.g. rectal bleeding, abdo mass). Other symptoms that aren't colorectal specific may be more appropriately investigated on the NSS pathway. Having a general option for GPs to refer when FIT is negative (and without 'red flag' symptoms) may result in significantly increased numbers of patients being referred on the colorectal pathway. This could then increase waiting times for patients at the highest risk.	Thank you for your comment. Recommendation 1.3 has been clarified to now state, “For people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)”. The committee felt that FIT was still appropriate for people with rectal bleeding. The committee agreed that a referral on a suspected cancer pathway was more likely for people with an abdominal mass, but that since it is not a specific

Comment number	Name and organisation	Section number	Comment	NICE Response
				symptom of colorectal cancer, a FIT result would still be useful to make sure that the person has the most appropriate investigation. So, the recommendation is still to offer FIT to people with abdominal mass alongside referral to secondary care. See section 3.3 for more details.
63 part 3	Web comment Stockport NHS FT		The committee have made many decisions made on opinions or what they think would be preferred and not evidence. I would suggest that where it is only opinion this should be specifically graded as not evidence and a stance should actually be not give an opinion in the guidelines; as there is no evidence to decide either way. Doing this is making a positive decision acting like a judge and jury with no evidence to support the stance. I think there needs to be a local approach agreed with all stakeholders locally. Safety netting seems to have been left to a local approach I think this should also occur with how regions use the FIT result if relative t the method. However the guidelines should make it clear that a local forum should be pulled together with stipulated stakeholders to discuss this and include the decision on cutoffs and if 1 or 2 samples are used.	Thank you for your comment. The committee often makes decisions based on uncertain evidence and have to make decisions based on what is available. The committee take into account the contributions of experts and are careful to make research recommendations where there are significant uncertainties. Please see section 6 in the NICE health technology evaluations manual. The decision question the committee was asked to address in the scope was "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…" and the intervention defined as "FIT using specific thresholds of haemoglobin per g of faeces to guide referral." So, specific thresholds needed to be defined. The committee felt that the potential drawbacks of dual FIT were likely to outweigh the benefits of increased sensitivity. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making (see sections 3.15 and 4.2).
69	Web comment	3.7	This clarity on dual FIT is welcomed and was positively viewed by primary care clinicians.	Thank you for your comment.

Comment number	Name and organisation	Section number	Comment	NICE Response
	Humber and North Yorkshire Cancer Alliance			
81 part 1	Web comment Cancer Research UK	1.6	In addition, further evidence is needed to clarify: 1. The role of dual FIT There are different approaches to dual FIT – one in which the patient is given multiple FITs at once and asked to complete them with separate bowel motions (replicate FIT), the where a second FIT is requested after the initial FIT result is received (repeat FIT). The evidence base mostly focuses on replicate FIT , , , , , and while this increasingly suggests increased sensitivity when replicate FIT is used, , the evidence base is mixed. It is unclear how replicate FIT and repeat FIT compare in terms of clinical and cost- effectiveness and acceptability, with larger studies needed to provide more definitive evidence.	Thank you for your comment. The terminology on dual FIT (termed replicate FIT in this comment) and repeat FIT has been clarified in section 3.10 of the guidance. The committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making (see section 4.2).
84 part 4	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)		Member E; Emphasises that doing two FIT's is not inequitable.	Thank you for your comment. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. So, the committee recommended further research on how using dual FIT in primary care affects test access, uptake and clinical decision making. Please see section 3.11 and 4.2 of the guidance for more detail.
90	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.7	Member A; I would question the use of "dual FIT" nomenclature. Why introduce a term not widely used in laboratory medicine? I recommend the use of "replicate FIT" for when two samples are taken to make an initial diagnostic decision and "repeat FIT" when a second sample is requested from a patient after a period to confirm or refute an initial result. This is well described in doi: 10.1177/00045632221096036. Member B; (Note: Member B has already submitted their personal response separately, the comments herein is a summary of their personal submission) Argued that a 2 FIT approach is safety netting. There is no evidence that 2 FIT testing could create inequality in access. Evidence shows that a two FIT approach increases sensitivity, increases specificity and the NPV of two negative FITs with normal haemoglobin allows for reduced referral. Thus it could be argued that a single FIT approach will create inequality in access to further diagnostics A two FIT approach would not put pressure on GPs or would complicate referral	Thank you for your comment. The committee acknowledged the potential confusion that could be caused by the term 'dual FIT' so clarification has been added in section 3.10 of the guidance. Committee felt that 'replicate FIT' could be interpreted to mean repeating the test on the same sample. The committee considered evidence that dual FIT (where either result being positive is a signal for referral) generally improved sensitivity but decreased specificity. The external assessment group commented that it did not identify any studies that demonstrated that specificity was increased by use of dual FIT when interpreting

Comment number	Name and organisation	Section number	Comment	NICE Response
			decisions Member E; Performing two FITs is not inequitable. There is evidence that 95% of patients asked to complete two tests did so and it is built-in safety netting. Our study highlighted the sampling error with one FIT and the chance of missing cancers with intermittent bleeding by just using one FIT. (A cohort study of duplicate faecal immunochemical testing in patients at risk of colorectal cancer from North-West England. BMJ 2022; 12:e059940.doi:10.1136/bmjopen-2021-059940)	"either test positive" as a positive test, and when comparing results for dual FIT to single FIT at the same threshold in the same study. So, using dual FIT could reduce the risk of missing people with cancer but would lead to further colonoscopies. However, the evidence on test uptake with dual FIT was from secondary care so may not be generalisable to primary care. The committee was concerned that asking for 2 tests could disadvantage groups that are already less likely to return samples and introduce additional implementation issues. The external assessment group noted that the Hunt study which is the source of the '95% returned 2 tests' figure did not provide the number of people who were asked to complete a FIT but did not return any samples. Further research was therefore recommended on how using dual FIT in primary care affects test access, uptake and clinical decision making. For more detail please see sections 3.11, 3.15 and 4.2 in the guidance.

THEME: Choice of tests

Comment number	Name and organisation	Section number	Comment	NICE Response
17	BSG	1.1	1.1 The BSG support this recommendation. However given the evidence base has been developed using the 2x analysers included, it may be more difficult to generate future data about the analysers not included, or data which compares different analysers.	Thank you for your comment. The committee considered the available data on the other tests included in the assessment, and concluded that there was too much uncertainty to make a positive

Comment number	Name and organisation	Section number	Comment	NICE Response
				recommendation. Please see section 3.6 of the guidance for more detail.
29	Web comment Sysmex and Sentinel	1.7 Further research is recommended (see the section on further research) on the effectiveness of:FOB Gold	Further FOB Gold data evidence is available in up to 14 references. Please refer to chapter 3.3.	Thank you for your comment. The external assessment group considered the evidence submitted and found that 1 study met their inclusion criteria (Jordaan et al. 2022). This was included in updated analyses which were presented to the committee. Although the uncertainty in the estimates of specificity were reduced, the committee felt that the sensitivity was too uncertain. So, the recommendation for further research was not changed. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.
30	Web comment Sysmex and Sentinel	3.3 For FOB Gold, 3 studies were identified, but these were small studies and the estimates of accuracy were uncertain. The committee acknowledged that FOB Gold was recommended in NICE's diagnostics guidance on quantitative FIT to guide referral for colorectal cancer in primary care (DG30).	A Word file document was submitted to NICE in August 2022 (+ DAP50 request for information FOB Gold_25.3.20_FINAL x modifica 2022_16032022_15082022) providing 11 references for FOB Gold in symptomatic population at that time. On top of this we would like to update with 3 more references: (1) A presentation from the WEO CRC meeting (San Diego May 2022): "Use of FIT in symptomatic patients" about the FOB Gold FITNESS trial in the Netherlands (manuscript ready for submission now). The goal was to evaluate the sensitivity for CRC of two FITs in symptomatic patients referred for colonoscopy (dual FIT approach). (2) Another published FOB Gold study from 2023: Maclean et al. (2023): "Efficacy and accuracy of faecal sampling by a digital rectal examination for FIT". (3) Unpublished data but manuscript available for FOB Gold implementation for investigating patients with lower GI symptoms associated with a low risk of CRC at the Mid Yorkshire Hospitals NHS Trust: Jordaan et al. (2022): "Development of a primary care pathway for using a FIT to triage patients presenting with bowel symptoms". As we cannot upload here references we would like to send you those per email to the 'Diagnostics@nice.org.uk' address with a remark to this comment section.	Thank you for your comment. The external assessment group considered the evidence submitted and found that 1 study met their inclusion criteria (Jordaan et al. 2022). This was included in updated analyses which were presented to the committee. Although the uncertainty in the estimates of specificity were reduced, the committee felt that the sensitivity was too uncertain. So, the recommendation for further research was not changed. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.

Comment number	Name and organisation	Section number	Comment	NICE Response
31	Web comment Sysmex and Sentinel	3.7	A presentation from the WEO CRC meeting (San Diego May 2022): "Use of FIT in symptomatic patients" about the FOB Gold FITNESS trial in the Netherlands (manuscript ready for submission now). The goal was to evaluate the sensitivity for CRC of two FITs in symptomatic patients referred for colonoscopy (dual FIT approach).	Thank you for your comment. The external assessment group considered the evidence submitted and found that 1 study met their inclusion criteria (Jordaan et al. 2022). This was included in updated analyses which were presented to the committee. Although the uncertainty in the estimates of specificity were reduced, the committee felt that the sensitivity was too uncertain. So, the recommendation for further research was not changed. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.
32	Web comment Sysmex and Sentinel	4.1 Further research is recommended to assess the effectiveness (including diagnostic accuracy, failure rate and test uptake) of:FOB Gold	FOB Gold data evidence is available in up to 14 references. Please refer to chapter 3.3.	Thank you for your comment. The external assessment group considered the evidence submitted and found that 1 study met their inclusion criteria (Jordaan et al. 2022). This was included in updated analyses which were presented to the committee. Although the uncertainty in the estimates of specificity were reduced, the committee felt that the sensitivity was too uncertain. So, the recommendation for further research was not changed. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.
48 part 7	Web comment (ACPGBI)		1.7 ACPGBI supports this recommendation although use of analysers other than HM-JACK and OC-Sensor may be more limited if not recommended for use for Quantitative FIT testing (as per Recommendation 1.1)	Thank you for your comment. The committee considered the available data on the other tests included in the assessment, and concluded that there was too much uncertainty to make a positive recommendation. Please see section 3.6 of the guidance for more detail.
63 part 2 and 4	Web comment Stockport NHS FT		In regards to cost effectiveness and pricing - the only suppliers recommended are the ones where you need to buy and interface separate equipment at the cost of around £100k. Other supplier like FOB-Gold reagents are available to be put on common analysers already present in current hospital labs making it far more expensive to introduce the only recommended tests. Is there money to help any lab change if they need to? Also there is a table 48 in the document stating the cost per test. This in not my experience going to the market place.	Thank you for your comment. The costs used in the external assessment group's report were provided by the manufacturers who were asked the cost of the technology, consumables, maintenance and any other relevant costs. The external assessment group note that no manufacturers reported the costs of the analysers separately so it was assumed that the per-test

Comment number	Name and organisation	Section number	Comment	NICE Response
			The document states that there is no adequate studies for some of the FIT assays and therefore this means they are not proven to be of use. This is illogical. In lab medicine all methods evolve with different reagents and we do not carry out full clinical studies to ensure that the evidence is still there for the use of the test. Generally we do a comparison with the new assay against the old assay and make correlations of how the new test will function and if we need to change a cut off – this happens a number of times annually for a number of tests and we are currently doing it for Vitamin D and B12 in my lab at the moment. With the following statement in the text how can there be a recommendation on any assay and cut-ff? The EAG stated that the broad conclusion that FIT is cost effective is robust, but this is a result of a cost saving at the expense of a small loss in health. Because of the similarity in results, the simplifications made in modelling, and the uncertainty in many of the model inputs, the EAG stated that it was not possible to clearly identify a specific FIT device and threshold that would be most cost effective. Choice of testing strategy is likely to depend on other factors important to people with gastrointestinal symptoms and healthcare professionals, such as the time to diagnosis or level of referrals.	cost included the cost of the analyser. Sources of funding for implementing testing are outside the remit of NICE guidance, although NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice. Please note that NICE's diagnostics guidance does not come with a funding requirement. The decision question the committee was asked to address in the scope was "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…" and the intervention defined as "FIT using specific thresholds of haemoglobin per g of faeces to guide referral." So, specific thresholds needed to be defined. The committee noted that methods for technical validation of FIT devices needed to be improved to allow for comparative data to be generated without the need for large clinical trials (see section 3.5 in the guidance).
82	Web comment Cancer Research UK	1.7	We agree there is a need to robustly evaluate point-of-care FIT. While these tests have the potential of to enable rapid FIT results, they are available to buy by the public, despite the limited evidence base supporting their use , similar to that for sampling by a digital rectal examination for FIT. (30,31) (30) Maclean, William, Zahoor, Zahida, O'Driscoll, Shane, Piggott, Carolyn, Whyte, Martin B., Rockall, Timothy, Jourdan, Iain and Benton, Sally C.. "Comparison of the QuikRead go® point-of-care faecal immunochemical test for haemoglobin with the FOB Gold Wide® laboratory analyser to diagnose colorectal cancer in symptomatic patients" Clinical Chemistry and Laboratory Medicine (CCLM), vol. 60, no. 1, 2022, pp. 101-108. https://doi.org/10.1515/cclm-2021-0655 (31) Maclean W, Benton SC, Whyte MB, Rockall T, Jourdan I. Efficacy and accuracy of faecal sampling by a digital rectal examination for faecal	Thank you for your comment.

Comment number	Name and organisation	Section number	Comment	NICE Response
			immunochemical testing. Annals of Clinical Biochemistry. 2023;60(3):169-176. doi:10.1177/00045632231155021	
84 part 3	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)		Member D; Has concerns that there is only two methods included in the guidance, and that FOB gold method has been dropped from the previous guidance.	Thank you for your comment. The committee acknowledged that FOB Gold was recommended in NICE's original diagnostics guidance on quantitative FIT to guide referral for colorectal cancer in primary care (DG30). During development of DG30 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 DG30. But the FOB Gold evidence base remained limited. This concern remained even with updated analyses provided by the external assessment group which used newer data. So, further research on FOB Gold was recommended. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.
93 part 3	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	5	Member D;.Concerns that only two methods are recommended in DAB 50, as the previous DG30 had 3 methods (OC-Sensor, HM-Jack, and FOB gold). Concern that only two methods will not be of benefit in the long term due to less testing options & less scope to offer services in different ways such as NPT FIT. Concerned that the lack of commercial competition will drive up costs, and will become very difficult for the other companies to generate an evidence base. Two methods recommended have the most evidence base in symptomatic patients. Concern that this may be directly due to market share rather than better test performance.	Thank you for your comment. The committee acknowledged that FOB Gold was recommended in NICE's original diagnostics guidance on quantitative FIT to guide referral for colorectal cancer in primary care (DG30). During development of DG30 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 DG30. But the FOB Gold evidence base remained limited. This concern remained

Comment number	Name and organisation	Section number	Comment	NICE Response
				even with updated analyses provided by the external assessment group which used newer data. So, further research on FOB Gold was recommended. Please see the external assessment report addendum 3 and section 3.6 of the guidance for more detail.

THEME: Choice of threshold

Comment number	Name and organisation	Section number	Comment	NICE Response
63 part 1 and 4	Web comment Stockport NHS FT		There is currently no harmonisation or standardisation of FIT methods, and no single primary reference material exists as yet, meaning that results from different methods are unlikely to give the same result. This is common in the diagnostic industry and is why there are method related reference intervals. Other NICE guidelines do not stipulate a cut-off for an assay and the cutoff can change with new evidence and depending what is desired. I think it is unwise to put a number in the clinical environment as this is not an absolute - you need to use the method related cut-off for the purpose of the test - hence there is a different cut off for asymptomatic screening programs. There is NICE guidelines for diagnosing coeliac disease or MI however they only stipulate that a lab must be ISO accredited and should use an appropriate assay. All the troponin assays and TTG assays use different cutoffs as there is not standardisation, the same should apply for FIT testing and not just recommend 2 assays- this is not analytically scientific or sound in regards to the market. It should be noted that most results in the symptmatic group (85% using the HM-Jack and undetectable by FOB Gold, HM-Jack and OC-Sensor - there is a minority of results around the 10ug/g level +/- 3ug/g. In the symptomatic population using a cut-off of 10 ug/g the positivity rate of the HM-	Thank you for your comment. The committee acknowledged that there is no universal reference standard for FIT, which makes it challenging to generate comparative data for different FIT devices. However, the decision question the committee was asked to address in the scope was "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…" and the intervention defined as "FIT using specific thresholds of haemoglobin per g of faeces to guide referral." So, specific thresholds needed to be defined. The committee noted that methods for technical validation of FIT devices needed to be improved to allow for comparative data to be generated without the need for large clinical trials. For more detail please see section 3.5 of the guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
			Jack is 16% and FOB gold is 13%, however adjusting the FOB gold cut off could make these results agree. With the following statement in the text how can there be a recommendation on any assay and cut-ff? The EAG stated that the broad conclusion that FIT is cost effective is robust, but this is a result of a cost saving at the expense of a small loss in health. Because of the similarity in results, the simplifications made in modelling, and the uncertainty in many of the model inputs, the EAG stated that it was not possible to clearly identify a specific FIT device and threshold that would be most cost effective. Choice of testing strategy is likely to depend on other factors important to people with gastrointestinal symptoms and healthcare professionals, such as the time to diagnosis or level of referrals.	
88	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.3	3.3 Member A;..The fact that different FIT systems give different numerical data for f-Hb is very important. There is now considerable evidence on this subject, including in the use of FIT in assessment of patients presenting with symptoms - 10.1515/cclm-2020-1170. I suggest that a stronger statement including the fact that "published data from different systems may not be transferable to other systems" should be included. It should also be noted that manufacturers "improve" their systems with time, for example in developing new buffers for the specimen collection devices (not tubes) that enhance haemoglobin stability: thus, data from a single system may not be transferable over time.	Thank you for your comment. The committee noted recent evidence that different tests produce different results from the same samples, and concluded that equivalence between brands could not be assumed. Please see section 3.5 of the guidance for more detail.
91 part 1 and 3	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.12	3.12 Member A; The document states "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." However, there is considerable evidence that use of f-Hb thresholds less than 10 µg Hb/g faeces lead to netter diagnostic sensitivity, albeit with lesser specificity. Perhaps the use of the limit of detection rather than the limit of quantitation (with proper reporting of results as documented above) requires further consideration. … Member B; I support the threshold of 10 and would not want in increased without further evidence.	Thank you for your comment. The committee considered this point, but did not change their recommendation, noting that thresholds below 10 micrograms per gram were less cost-effective than 10 or higher. The committee was concerned that confidence in the test would deteriorate at thresholds higher than 10, so further research was recommended to determine how higher thresholds would affect decision making and clinical outcomes. For more detail see sections 3.17. 3.18 and 4.1

THEME: Research considerations

Comment number	Name and organisation	Section number	Comment	NICE Response
37	Web comment (organisation not stated)	1.6 Further research	I would suggest that further research is required on the use of FIT (along with other tests/algorithms) to triage patients for risk. Many trusts struggle to meet the 2 week target and FIT etc may assist in triage and identify high (and low) risk patients. A simple AI approach based on FIT, HB, age etc could be created to triage patients based on risk. In addition more research should be performed using ROC curves for thresholds versus CRC and large polyps.	Thank you for your comment. The use of FIT as a triage tool in secondary care is outside the scope of this assessment, which is only focused on FIT in primary care to guide referral decisions. ROCs were generated by the external assessment group as part of their report (see figures 5-8 in the external assessment report), but the committee considered cost-effectiveness and other factors in their decision as well as accuracy. The committee considered that FIT could be used as part of a risk algorithm, but noted that the ongoing COLOFIT project is investigating this and no further research was recommended. NICE intends to assess the COLOFIT algorithm (see GID-HTE10011).
47	Web comment (organisation not stated)	4.2 Further research is recommended on how using thresholds higher than 10 micrograms of haemoglobin per gram of faeces would affect decision making and clinical outcomes.	i would suggest further research on thresholds and to undertake ROC curves on ascertaining a level that does not miss CRC or large polyps. In addition, linked with haemoglobin and other parameters, a risk based triage should be developed to optimise waiting lists.	Thank you for your comment. Thank you for your comment. The use of FIT as a triage tool in secondary care is outside the scope of this assessment, which is only focused on FIT in primary care to guide referral decisions. ROCs were generated by the external assessment group as part of their report (see figures 5-8 in the external assessment report), but the committee considered cost-effectiveness and other factors in their decision as well as accuracy. The committee considered that FIT could be used as part of a risk algorithm, but noted that the ongoing COLOFIT project is investigating this and no further research was recommended. NICE intends to assess the COLOFIT algorithm (see GID-HTE10011).
51	Bowel Cancer UK	6.1	Thresholds for referral It is stated that 'two thresholds could be used to define low, intermediate and high risk populations'. There is limited research on this, but the use of different thresholds	Thank you for your comment. The committee considered strategies that used 2 thresholds, but felt that they would unnecessarily complicate referral decisions, and were likely to be less cost-

Comment number	Name and organisation	Section number	Comment	NICE Response
			should be investigated as part of a research project to improve the risk stratification of FIT.	effective than using a single threshold. Please see section 3.16 in the guidance for more detail.
73	Web comment Humber and North Yorkshire Cancer Alliance	4	It is suggested that further research into the use of FIT in younger patients where the pre-test probability of cancer is lower and IBD prevalence is higher in terms of how to use faecal biomarkers would be useful.	Thank you for your comment. An additional research recommendation for use of FIT in people aged under 40 has been added (see section 3.7 and 4.3 for more detail)
81 part 2	Web comment Cancer Research UK	1.6	In addition, further evidence is needed to clarify: 2. The impact of combining FIT with other tests, including FIT in risk stratification algorithms or tailored FIT thresholds according to patient characteristics. While the evidence is base is still emerging, there is some evidence to suggest benefit of combining FIT with blood tests, using FIT within a risk algorithm, or adopting varying FIT thresholds depending on patient characteristics. Other research suggests little to no added benefit above using FIT alone. (21-29) (21) Farkas NG, Fraser CG, Maclean W, Jourdan I, Rockall T, Benton SC. Replicate and repeat faecal immunochemical tests in symptomatic patients: A systematic review. Ann Clin Biochem. 2022 May 5:45632221096036. doi: 10.1177/00045632221096036. (22) Hunt N, Rao C, Logan R, et al. A cohort study of duplicate faecal immunochemical testing in patients at risk of colorectal cancer from North-West England. BMJ Open 2022;12:e059940. doi: 10.1136/bmjopen-2021-059940 (23) Farkas NG, O'Brien J, Whyte M, Jourdan I, Rockall T, Benton SC. An observational study of replicate faecal immunochemical tests in the urgently referred symptomatic cohort. Annals of Clinical Biochemistry. 2023;0(0). doi:10.1177/00045632231163425 (24) A D Gerrard and others, Double faecal immunochemical testing in patients with symptoms suspicious of colorectal cancer, British Journal of Surgery, Volume 110, Issue 4, April 2023, Pages 471–480, https://doi.org/10.1093/bjs/znad016 (25) Johnstone, MS, MacLeod, C, Digby, J, Al-Azzawi, Y, Pang, G, Watson, AJM, Prevalence of repeat faecal immunochemical testing in symptomatic patients attending primary care. Colorectal Dis. 2022; 24: 1498– 1504. https://doi.org/10.1111/codi.16240 (26) Crooks, CJ, Banerjea, A, Jones, J, Chapman, C, Oliver, S, West, J, et al. Understanding colorectal cancer risk for symptomatic patients in primary care: A	Thank you for your comment. The committee considered that FIT could be used as part of a risk algorithm, but noted that the ongoing COLOFIT project is investigating this and no further research was recommended. NICE intends to assess the COLOFIT algorithm (see GID-HTE10011).

Comment number	Name and organisation	Section number	Comment	NICE Response
			cohort study utilising faecal immunochemical tests and blood results in England. Aliment Pharmacol Ther. 2023; 00: 1– 10. https://doi.org/10.1111/apt.17632 (27) Johnstone MS, Burton P, Kourounis G, Winter J, Crighton E, Mansouri D, Witherspoon P, Smith K, McSorley ST. Combining the quantitative faecal immunochemical test and full blood count reliably rules out colorectal cancer in a symptomatic patient referral pathway. Int J Colorectal Dis. 2022 Feb;37(2):457-466. doi: 10.1007/s00384-021-04079-2. (28) Ayling, R.M., Lewis, S.J. and Cotter, F. (2019), Potential roles of artificial intelligence learning and faecal immunochemical testing for prioritisation of colonoscopy in anaemia. Br J Haematol, 185: 311-316. https://doi.org/10.1111/bjh.15776 (29) Withrow, D.R., Shine, B., Oke, J. et al. Combining faecal immunochemical testing with blood test results for colorectal cancer risk stratification: a consecutive cohort of 16,604 patients presenting to primary care. BMC Med 20, 116 (2022). https://doi.org/10.1186/s12916-022-02272-w	
84 part 2	Web comment (BM) ACB - Scientific Affairs and Clinical Practice (SACP)		Opening Comments Member C; States the DAB 50 is generally sound but light on analytical aspects so recommends further research into this area.	Thank you for your comment. The committee considered that recommendations on specific analytical aspects of FIT are outside the usual scope of NICE guidance. However, NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
85	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	1.7	1.7 Member A; I agree that it would be of value to have further information on the use of automated systems in the application of FIT in the assessment of patients presenting with lower bowel symptoms. However, I think that rapid turnaround time from sample collection to result reporting is vital. Thus, I cannot support the idea that ELISA systems deserve further study. Although there is already considerable evidence on outcomes using faecal haemoglobin concentration (f-Hb) thresholds above 10 µg Hb/g faeces from Scotland using HM-JACKarc, I do agree that further data using other immunoturbidimetric FIT systems on this subject would be valuable	Thank you for your comment.
89	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.4	Member A; I think an opportunity is being missed here. It is well documented in a comprehensive recent review that women are seriously disadvantaged in CRC screening using FIT - doi: 10.1515/cclm-2022-0583. I think that the material documented in this review should be considered, especially the use of sex partitioned f-Hb thresholds, particularly since a recommendation is to research f-Hb thresholds greater than 10 µg Hb/g faeces. I should like to see “the effect of using different f-Hb thresholds in men and women” as an important research requirement.	Thank you for your comment. The external assessment group looked for evidence on diagnostic accuracy by sex in a symptomatic population presenting to primary care. The results were varied but in some studies sensitivity and specificity were higher in women than in men (see section 4.3.12.3 in the external assessment

Comment number	Name and organisation	Section number	Comment	NICE Response
			3.4 Member A; Further, although algorithms have been developed, as documented in the review, these have not proven successful to date. In addition, there is literature on the use of additional tests such as urinary volatiles - doi: 10.1016/j.ejca.2023.03.002 – and calprotectin and M2-PK: should DAB50 document and discuss such approaches?	report). The committee concluded that it was not possible to make any recommendations on whether FIT should be used differently by sex (see section 3.7 in the guidance for more detail). The committee considered that FIT could be used as part of a risk algorithm, but noted that the ongoing COLOFIT project is investigating this and no further research was recommended. NICE intends to assess the COLOFIT algorithm (see GID-HTE10011). The use of tests other than FIT is out of the scope of this assessment.
92	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	4.1	Member B; I would suggest that further research is required on the use of FIT (along with other tests/algorithms) to triage patients for risk. I propose central funding to ensure laboratory compliance with the service Member C;. Recommends further research into pre-analytical, analytical and post analytical aspects of FIT as follow; Pre-analytical: The devices used for collection are all slightly different. Whilst work has been undertaken on this, I do not think we fully understand the contribution their use has to the imprecision on the results we get. Which is the optimal collection device?, how does its ease of use vary between patient groups? – I guess I think mainly of elderly patient as this question has arisen quite a lot from GP's. Also how does the sampling vary with sample consistency differences. So – how/can we get some additional evidence?	Thank you for your comment. The committee considered that FIT could be used as part of a risk algorithm, but noted that the ongoing COLOFIT project is investigating this and no further research was recommended. NICE intends to assess the COLOFIT algorithm (see GID-HTE10011). Guidance on sources of funding are outside the remit of NICE guidance. The committee considered that recommendations on specific analytical aspects of FIT are outside the usual scope of NICE guidance. However, NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice. A recommendation was made to investigate methods to improve access, uptake and return of FIT in groups in which engagement is less likely, which includes people with dexterity issues (see recommendation 4.4)
99	Web comment (organisation not stated)	1.6	Could we please add a third and 4th bullet point about future research which is: (1) to determine the miss rate for colorectal cancers when a FIT score is <10 and (2)to determine the overall impact on stage at diagnosis for colorectal cancers after recommending that patients are selected for an urgent suspected cancer referral to Secondary Care only when their FIT score is 10 or more (excluding anal mass, abdominal mass and rectal mass)?	Thank you for your comment. The external assessment group note that the miss rate for colorectal cancer at a threshold of 10 micrograms per gram can be calculated as 100% minus the sensitivity of the test. The committee did not make a recommendation for research on the stage at

Comment number	Name and organisation	Section number	Comment	NICE Response
			These two items will be considered important to patients and their advocates. Many thanks	diagnosis, but please note that people without FIT results or with a FIT below 10 micrograms per gram can still be referred on a suspected cancer pathway if there is strong clinical concern of cancer because of ongoing unexplained symptoms (please see recommendation 1.3).

THEME: Equalities considerations

Comment number	Name and organisation	Section number	Comment	NICE Response
53	Bowel Cancer UK	7	Potential equality issues The guidelines on FIT in patients with signs and symptoms of suspected CRC from the ACPGBI and the BSG included reference to studies which report the uptake of FIT in symptomatic populations as between 78.9% and 94% (Monahan KJ, Davies MM, Abulafi M, et al, 2022). 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 within this assessment. According to research conducted by Thoughtful Content and Research Your Way on behalf of Bowel Cancer UK, many people with disabilities face accessibility issues when attempting to use FIT kits. One participant stated: “As a person with severe sight loss (blind), it has proven difficult to complete the test independently without sighted support. As you can imagine, this can lead to the feeling of degradation when asking a carer\friend to help with this. I would like to see how an easier method of taking the sample without such support. For an example, the use of a small spoon and test tube, rather than the current test implement”. The difficulty faced by those with disabilities or dexterity issues in completing a FIT should be adequately addressed within this assessment so that patients are referred appropriately when they are unable to complete a FIT kit.	Thank you for your comment. Recommendation 4.4 for social research on ways to improve access, uptake and return of FIT has been expanded to include younger people, and the description of physical disabilities now includes specific reference to visual impairment and reduced dexterity. Additionally, recommendation 1.3 stipulates that people who are do not return a FIT can still be referred if there is strong clinical concern of cancer, and recommendation 1.5 states that clinicians should consider if people may need additional help, information or support to return their sample. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
65	Web comment Humber and North Yorkshire Cancer Alliance	1.5	This recommendation is very broad and somewhat vague. Patients at risk here might range from those with dexterity or mechanical strength issues, through to those living in social situations which make completing a test challenging, and covering an array of other issues between. There is too much wrapped up in this point for it not to be unpacked in some way.	Thank you for your comment. Recommendation 4.4 for social research on ways to improve access, uptake and return of FIT has been expanded so that the description of physical disabilities now includes specific reference to visual impairment and reduced dexterity. Recommendation 1.5 now

Comment number	Name and organisation	Section number	Comment	NICE Response
				states that clinicians should consider if people may need additional information as well as help or support to return their sample. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
74	Web comment Humber and North Yorkshire Cancer Alliance	4.3	This proposal is very welcome but should be widened to include a broader spectrum of issues faced by patients, such as those who cannot understand the instructions, patients who lack the mechanical strength in their fingers to close and open the device, those living independently with physical disabilities, including visual impairments.	Thank you for your comment. Recommendation 4.4 for social research on ways to improve access, uptake and return of FIT has been expanded so that the description of physical disabilities now includes specific reference to visual impairment and reduced dexterity. Recommendation 1.5 now states that clinicians should consider if people may need additional information as well as help or support to return their sample. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
75	Web comment Cancer Research UK	1	We're unaware of any evidence on this specifically for symptomatic patients but there is evidence to show that people with learning disabilities are less likely to take up screening. There are some resources for health professionals to support people with a learning disability in the screening context; similar resources might be considered to support patients with symptoms. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0043841 https://phescreening.blog.gov.uk/2020/01/31/bowel-cancer-screening-new-information-for-people-with-learning-disabilities/	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
76 part 3	Web comment Cancer Research UK	1.1	The evidence base suggests that there are differences between some demographic groups in preferences, attitudes, barriers to completing FIT and information needs and preferences. In a survey of 260 people, researchers found that increased area-level deprivation was associated with decreased satisfaction with the GP consultation relating to FIT and how they received their results . There were reports of 'not knowing the purpose of the test' which caused 'anxiety' and 'confusion', leading to dissatisfaction. (2)	Thank you for your comment. Recommendation 4.4 asks for social research to improve access, uptake and return of FIT, especially in groups in which engagement is less likely. These include people with lower socioeconomic status, people form ethnic minorities and younger people. The committee also noted that certain groups may need tailored resources or additional support to

			Insights from Cancer Research UK's July 2022 Public Omnibus survey further underline the importance of providing patients with clear information on the purpose of FIT to support uptake. In the July 2022 Public Omnibus, we asked respondents what would make them more likely to complete a FIT. The most endorsed prompts were related to clear guidance on how to take the test (34%) and clear explanations as to why they should do it via their GP/doctor (3 2%) or generally by having more information about why the test is important (25%) (3). These survey results also indicate that negative attitudes towards FIT may be more pronounced in certain demographic groups. For example, in the Cancer Research UK July 2022 Public Omnibus, a higher proportion of ethnic minority respondents cited 'embarrassment' (14% versus 9% of White respondents) and 'finding the test too messy' (13% versus 6% of White respondents) as hypothetical barriers to completing a FIT. The latter statistic is consistent with results from the Cancer Research UK 2023 Cancer Awareness Measure into bowel screening barriers, where people from Black and ethnic minority backgrounds were more likely to be put off completing the bowel screening test because they found it too messy to complete (7% versus 3%). While this statistic is about FIT in a screening rather than a symptomatic context, there is an interesting parallel across the two uses, which should be explored further. More research is needed to better understand the prevalence of other barriers amongst different population groups, and how they can be addressed through tailored interventions. (4,5) The NICE FIT study patient survey which found willingness to do FIT again was stronger in patients from White compared with other non-White groups, and in those outside London . Additionally, preference for FIT over colonoscopy was weaker in younger age groups (those 40-64 compared to those >65). The researchers did not have ethics approval to collect demographic data on patients who declined to return a FIT, so could not comment on whether some people are more or less likely to return a FIT when asked to. This information is not routinely reported in research and evaluations as far as we are aware, but we would be keen to see this addressed in the future. We recommend that further intelligence on FIT barriers within specific patient cohorts is gathered and used to develop tailored interventions that support equitable access to, and successful completion of the test in all groups. (6) (1) Tibbs RE, Benton SC. A service evaluation of the use of faecal immunochemical tests in symptomatic patients aged under 50 years presenting to primary care. Annals of Clinical Biochemistry. 2023;0(ja). doi:10.1177/00045632231189386 (2) Gil, Natalie, Helen Su, Kirandeep Kaur, Michael Barnett, Anna Murray, Stephen Duffy, Christian von Wagner, and Robert S Kerrison. "Patient Experience and Satisfaction with Symptomatic Faecal Immunochemical Testing: An Explanatory	enable them to use the test (see section 3.1 of the guidance).

Comment number	Name and organisation	Section number	Comment	NICE Response
			Sequential Mixed-Methods Evaluation." British Journal of General Practice 73, no. 727 (2023): e104-e14. (3) All figures, unless otherwise stated, are from YouGov Plc. Total sample size was 2,119 adults. Fieldwork was undertaken between 11 – 12 July 2022. The survey was carried out online. The figures have been weighted and are representative of all adults in the UK (aged 18+). (4) All figures, unless otherwise stated, are from YouGov Plc. Total sample size was 2,119 adults. Fieldwork was undertaken between 11 – 12 July 2022. The survey was carried out online. The figures have been weighted and are representative of all adults in the UK (aged 18+). (5) Cancer Research UK's Cancer Awareness Measure survey (February 2023) Unpublished findings. Data collected by YouGov Plc. (6) Georgiou Delisle, Theo, Nigel D'Souza, Bethan Davies, Sally Benton, Michelle Chen, Helen Ward, and Muti Abulafi. "Faecal Immunochemical Test for Suspected Colorectal Cancer Symptoms: Patient Survey of Usability and Acceptability." BJGP Open 6, no. 1 (2022): BJGPO.2021.0102. Please note, we'd be happy to discuss the results of our omnibus surveys and the CAM, cited above, if helpful.	
77	Web comment Cancer Research UK	1.5	Health professionals should be made aware within the guidance of the patient groups who may face more barriers to completing FIT, according to the current evidence base. Please see responses to recommendation 1 and implementation	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

THEME: IBD

Comment number	Name and organisation	Section number	Comment	NICE Response
24	BSG IBD Committee	3.8 The EAG's clinical review found that the estimates of the diagnostic	Table 27: Summary sensitivity and specificity at selected thresholds for IBD outcomes The sensitivity and specificity for qFIT in IBD is lower than for the detection of cancer, as expected, ranging from overall sensitivity 72.9 (57.1,88.2) specificity 76.4 (59.2,92.1) at a FIT of 10. The HM-JACKarc performs better than the OC-Sensor	Thank you for your comment. The committee noted that NICE guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel is that calprotectin testing (2013) should be an option for people with lower gastrointestinal

Comment number	Name and organisation	Section number	Comment	NICE Response
		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 guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel).	test. The EAR has highlighted that the studies included had a high level of heterogeneity and therefore uncertainty. As a comparison the performance of Faecal Calprotectin in a meta-analysis has reported sensitivity (90.6%) was achieved at a cut-off 50 µg/g, whereas the best specificity (78.2%) was found at levels >100 µg/g. [Rokkas T, Portincasa P, Koutroubakis I. Fecal Calprotectin in Assessing Inflammatory Bowel Disease Endoscopic Activity: a Diagnostic Accuracy Meta-analysis. JGLD [Internet]. 30Sep.2018 [cited 13Jul.2023];27(3):299-06.DOI 10.15403/JGLD.2014.1121.273.PTI] Faecal calprotectin is not universally available in all four nations in primary or secondary care and has in some places been superseded by FIT. Therefore the generalisation that GPs are likely to order a faecal calprotectin simultaneously, is inaccurate (and counterintuitive) and in some areas not possible as the faecal calprotectin test has been restricted (as disease monitoring tool) in secondary care in patients with a known IBD diagnosis. What data is available to support the generalisation and more crucially, what advice regarding safety netting will be provided to minimise delays to the IBD diagnosis?	symptoms if cancer is not suspected, and that the focus of this assessment was using FIT to guide referral pathways for colorectal cancer. FIT is not intended to replace investigations for other pathology. The committee highlighted existing guidance on investigations for lower gastrointestinal symptoms 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's guidelines for the investigation of chronic diarrhoea or on the management of inflammatory bowel disease. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice. Please see sections 3.12 and 3.19 for more detail.
25	BSG IBD Committee	3.14 The committee discussed safety netting for people with negative FIT results and	In response to safety netting and comment 1 The option to offer a faecal calprotectin should be explicitly stated in the context of (negative FIT and) ongoing symptoms without a clear diagnosis.	Thank you for your comment. As no evidence was presented on the relative effectiveness of different forms of safety netting, the committee was unable to provide specific recommendations on implementation of safety netting. But, the committee discussed the different options for

Comment number	Name and organisation	Section number	Comment	NICE Response
		ongoing symptoms. 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.		safety netting that are available. NICE guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel is that calprotectin testing (2013) should be an option for people with lower gastrointestinal symptoms if cancer is not suspected. is that calprotectin testing should be an option for people with lower gastrointestinal symptoms if cancer is not suspected.
70	Web comment Humber and North Yorkshire Cancer Alliance	3.8	A laboratory manager commented on the assumption that GPs will probably order BOTH Faecal Calprotectin and FIT being potentially very wasteful of laboratory resource. It was noted that acknowledgement was needed that further research is required on the use of FIT in younger patients where the pre-test probability of cancer is lower and IBD prevalence is higher in terms of how to use faecal biomarkers. Excluding IBD following a FIT negative result has a role in the management of patients in a FIT negative pathway, particularly in a primary care 'watch and wait' scenario, so there is relevance in addressing the order and accuracy of FIT and calprotectin in these guidelines.	Thank you for your comment. NICE guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel is that calprotectin testing (2013) should be an option for people with lower gastrointestinal symptoms if cancer is not suspected. As no evidence was presented on the relative effectiveness of different forms of safety netting, the committee was unable to provide specific recommendations on implementation of safety netting. But, the committee discussed the different options for safety netting that are available. Please see sections 3.12 and 3.19 of the guidance for more detail.
94	Crohn's & Colitis UK	3.8 The EAG's clinical review found that the estimates of	We do not agree with this statement. Research commissioned by Crohn's & Colitis UK which analysed 38.3 million GP records from 2009 to 2019 found that less than 3% of people diagnosed with Inflammatory Bowel Disease between 2009 and 2019 had a recorded faecal calprotectin test in their GP record within the year before their diagnosis. Furthermore, we hear anecdotally that faecal calprotectin is not	Thank you for your comment. NICE guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel is that calprotectin testing (2013) should be an option for people with lower gastrointestinal symptoms if

Comment number	Name and organisation	Section number	Comment	NICE Response
		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. Because the focus of this assessment was using FIT to guide referral pathways for colorectal cancer, other methods of detecting IBD were not considered.	universally available in all four nations in primary or secondary care and has in some places been superseded by FIT. We would like to know what data NICE has used to support this statement. We maintain that to effectively triage patients for endoscopy and minimise the risk of diagnosis delays, that a national primary care pathway for patients presenting with lower gastrointestinal symptoms is required. As part of this pathway a consistent approach to the use of faecal calprotectin testing should be embedded as well as a clear referral pathway for patients with persistent lower gastrointestinal symptoms who do not meet the FIT threshold for referral.	cancer is not suspected. 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 pathology. As no evidence was presented on the relative effectiveness of different forms of safety netting, the committee was unable to provide specific recommendations on implementation of safety netting. But, the committee discussed the different options for safety netting that are available. Please see sections 3.12 and 3.19 of the guidance for more detail.
95	Crohn's & Colitis UK	3.14 The committee discussed safety netting for people	We believe that the option to offer a faecal calprotectin test should be explicitly stated in the context of negative FIT and ongoing symptoms. As per our previous comment, this would ensure that that GPs do offer a faecal calprotectin test should they suspect IBD.	Thank you for your comment. NICE guidance on faecal calprotectin diagnostic tests for inflammatory diseases of the bowel is that calprotectin testing (2013) should be an option for

Comment number	Name and organisation	Section number	Comment	NICE Response
		with negative FIT results and ongoing symptoms. 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.		people with lower gastrointestinal symptoms if cancer is not suspected. 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 pathology. As no evidence was presented on the relative effectiveness of different forms of safety netting, the committee was unable to provide specific recommendations on implementation of safety netting. But, the committee discussed the different options for safety netting that are available. Please see sections 3.12 and 3.19 of the guidance for more detail.
96 part 2	Web comment TVCA		2. Consideration should be given to the use of qFIT tests in patients with known IBD. This will very often be positive even when colitis is only marginally active and so does not add any useful information. Known IBD patients should already be on appropriate screening pathways and if there is a worrying change in symptoms then an urgent IBD followup should be requested rather than using a qFIT test which may put them on a unnecessary 2WW pathway which is then difficult to stop.	Thank you for your comment. A recommendation has been made for further research to determine how conditions that may increase the risk of gastrointestinal bleeding (such as IBD) affect the diagnostic accuracy of FIT. Please see sections 3.7 and 4.5 of the guidance for more detail.

THEME: Wording of recommendations

Comment number	Name and organisation	Section number	Comment	NICE Response
6	Web comment (organisation not stated)	1.3	The current phrasing of this sentence has the potential to dilute the benefits of FIT related to referral prioritisation and managing diagnostic capacity, as the use of symptom based referral criteria is so embedded. Would benefit from strengthening the message (as outlined in 2.4) that it is performed prior to referral for majority of cases	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
7	Web comment (organisation not stated)	1.7 'It is important that GPs can refer people without a positive FIT result'	See comment to 1.3 - current phrasing has potential to reduce this impact of this guidance due to embedded referral practice based upon symptoms. ?rephrase sentence - 'People who do not return faecal samples or have negative FIT results may still need further investigation in secondary care and it is important that GPs can still refer if necessary'	Thank you for your comment. The committee did not think that GPs would routinely refer people with symptoms without first requesting a FIT. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
8 part 1	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	1.3	In cases where there are no 'red flag symptoms', the FIT result should be waited for before referral to secondary care. As reflected in NHSEI letter 210922 to primary care (Publication reference: PR2005_i). To keep this sentence as it stands, is also in direct contradiction to current Cancer Waiting Time Guidance v11.1 section 6.7.3 and the BSG guidance it references: 'It is therefore recommended all GP practices follow the BSG/ACPGBI guidance and provide FIT testing for all patients with colorectal symptoms (bar those with anal/rectal mass or anal ulceration) prior to the referral to support appropriate decision making and to make sure for those referred the result is available in time for clinical triage and therefore allows for prompt decision making'.	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).

Comment number	Name and organisation	Section number	Comment	NICE Response
14	Web comment (organisation not stated)	1.3 'clinical'	This needs to be made clear that a FIT result is important as it can prevent a patient going straight to test, or delay them even further. So even if there is a clinical concern, the FIT result should have been completed as part of this to ensure secondary care have the full picture when vetting, to get them to the most appropriate place quickly.	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
15	Web comment (organisation not stated)	1.7	This is important but needs to balance with 1.3 - in that Secondary Care could triage the patient more quickly with a FIT result. Obviously cancers are found in negative FITs too but as long as the result or reason for not doing a FIT is on the referral, this would save time in the patient's care pathway.	Thank you for your comment. How secondary care triage people who have been referred is outside the scope of this assessment. Recommendation 1.3 is intended to cover people who are unable to complete a FIT in addition to those who don't return a sample for other reasons and those with a negative FIT with ongoing clinical concern.
26	Web comment Calderdale Cares Partnership	1.3	I feel that the suggestion to perform FIT pre 2ww referral should be made stronger as per the BSG guidance. Otherwise it will not be used effectively as a triage tool. Can we consider something along the lines of "All patients presenting with symptoms of suspected lower GI cancer should have a FIT test in order to guide urgency of referral". However, it is important that referrers have the ability to refer a patient either with a negative FIT test (if still concerned) or unable to perform a FIT test for whatever reason, this latter aspect is mentioned later in the document and feels sensible.	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
33 part 1	Web comment (organisation not stated)		I welcome this document. It is clear that a huge amount of work has been undertaken which re-enforces the use of FIT in low risk symptomatic adults. I support the cut-off of ten. However would suggest that NICE should re-emphasis that FIT Testing by GPs is for adults with low-risk symptoms. If we use a cut-off of 10 in asymptomatic patients then this will overwhelm endoscopy services.	Thank you for your comment. Recommendation 1.1 outlines the population that is eligible for FIT, which includes people with symptoms that would previously have been defined as 'low' or 'high' risk. People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme.
34	Web comment (organisation not stated)	1.1 Quantitative faecal immunochemical	There needs to be clarity between this document and NG12. This document clearly relates to adults with signs and symptoms (symptomatic) but NG12, 1.3.1 has the word "or" prior to "tests showing occult blood in faeces" which is being interpreted by	Thank you for your comment. The wording of NG12 will be updated simultaneously with the publication of this guidance to ensure that

Comment number	Name and organisation	Section number	Comment	NICE Response
		testing (FIT) using HM-JACKarc or OC-Sensor is recommended to guide referral for adults with signs or symptoms suggestive of colorectal cancer (as outlined in recommendations 1.3.1 to 1.3.4 in NICE's guideline on suspected cancer, excluding those with rectal mass).	some GPs that they can request FIT in asymptomatic patients. This ambiguity needs to be resolved as we are increasing getting FIT requests in asymptomatic patients who have "positive" FIT (but only slightly POS who go on the 2W pathway and nothing is found	recommendations are consistent across NICE publications. People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme.
35	Web comment (organisation not stated)	1.2 Refer adults using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they have a FIT result of at least 10 micrograms of haemoglobin per gram of faeces.	This sentence is ambiguous. FIT tests should only be requested in Symptomatic patients (outside the national screening programme). Suggest changing to "refer low risk symptomatic adults.....if they have a FIT result etc	Thank you for your comment. Recommendation 1.1 outlines the population that is eligible for FIT, which includes people with symptoms that would previously have been defined as 'low' or 'high' risk. People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme. Recommendation 1.2 applies only to people who have been offered a test under the conditions outlined in 1.1.
58	Web comment (organisation not stated)	1.7 People who do not return faecal samples or have negative FIT results may still need further investigation in secondary care. It is important that	This again appears contradictory. NHSE wrote to primary and secondary care asking for FIT to be used in primary care. Having a general statement in this section (regardless of whether it is explained in further detail in a later section), could lead to reduced utilisation of FIT and increased numbers of patients referring on colorectal pathways, increasing waiting times for patients at the highest risk.	Thank you for your comment. Recommendation 1.1 states that FIT should be used in people with particular symptoms. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… referral to an appropriate secondary care pathway should not be delayed if there is

Comment number	Name and organisation	Section number	Comment	NICE Response
		GPs can refer people without a positive FIT result if they think it is necessary.		strong clinical concern of cancer because of ongoing unexplained symptoms (for example, abdominal mass).
64	Web comment Cambridgeshire & Peterborough ICS		I request through this feedback that recommendation 1.3 in the draft be removed before the guidance is finalised. Recommendation 1.3 creates a conundrum for collaborative working between Primary Care and Secondary Care in the pathway to improving early diagnosis and to he detriment of achieving FDS. I have outlined my comments below for the reason for this feedback. Comment on page 3 of 22 The draft NICE FIT guidance recommendation 1.3 that referral to secondary care should not be delayed in the absence of a FIT result if there is clinical concern creates a grave confusion for Primary Care. Firstly, it doesn't align with the Network Contract DES IIF 2023-24, CAN-02: percentage of lower GI 2WW cancer referrals accompanied by FIT result, with the result recorded in the 21 days leading up to the referral. The draft FIT guidance doesn't align with the NHSE communication last year, to all GPs that all 2WW referrals are accompanied with a FIT. This link includes the letters sent to hospitals and GPs. https://www.england.nhs.uk/wp-content/uploads/2022/10/B2005_ii_Using-faecal-immunochemical-testing-lower-gastrointestinal-pathway_Secondary-care-letter.pdf Comment on page 4 of 22 There is no explanation why the committee made recommendation 1.3, although the draft outlines clearly the reasons for all the other recommendations I was given to understand that NICE have recommended implementation of the BSG guideline superseding pre-existing NICE guidelines. The draft NICE analysis undermines the BSG guidance through recommendation 1.3 and all the hard work that has gone to implement the NHSE letter and improve in FDS for lower GI 2ww pathways.	Thank you for your comment. Recommendation 1.1 states that FIT should be used in people with particular symptoms. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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). The committee did not think that GPs would routinely refer people with symptoms without first requesting a FIT. Recommendation 1.3 is intended to ensure equality of access to investigations for people who may not be able to complete a FIT. Further explanation of the committee's considerations for recommendation 1.3 can be found in sections 3.8 and 3.20 of the guidance.
66	Web comment	1.3	Discussions with primary care clinicians indicates that the language here is neither precise enough nor specific enough to avoid confusion. The need to be able to refer in the absence of a FIT result is clear and welcome, but this recommendation needs	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal

Comment number	Name and organisation	Section number	Comment	NICE Response
	Humber and North Yorkshire Cancer Alliance		more contextual wording to direct efforts to obtain a FIT result and the nature of the clinical concern. Clinicians took this recommendation as meaning they could refer as per existing NG12 guidelines without seeking a FIT result. The implication of the guidance is that GPs should attempt to get a FIT result before referring, but not delay a referral if that isn't forthcoming, or isn't anticipated to be forthcoming - this needs to be more explicitly stated if it is the intended meaning.	sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
93 part 1	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	5	General Comments Member B;. Sates the need to emphasis that the FIT use-case here is for low risk symptomatic patients. NG12 is ambiguous and GPS are requesting FIT in asymptomatic patients causing angst when someone is put on a 2 week wait and the only issue is a FIT of 17! This is resulting in a call to raise the threshold by secondary care- we need to stop this!	Thank you for your comment. Recommendation 1.1 outlines the population that is eligible for FIT, which includes people with symptoms that would previously have been defined as 'low' or 'high' risk. People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
96 part 1	Web comment TVCA		1.The problem with allowing ""high risk"" referrals prior to the result of the qFIT is that the time pressures on the secondary care pathway are such that the referral will often need to be triaged (either in clinic or virtually) before this result is available. Once a colonoscopy has been requested then it is difficult to stop it occurring if the qFIT test is subsequently returned as negative. The wait of a few days to get this result will not influence the outcome for the patient and would allow the GP to refer on the most appropriate pathway with all the information available	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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).
97	Web comment (organisation not stated)	1.3	This is quite right. Not all patients can or will return a FIT sample (e.g. patients with serious mental illness and difficult lives, those with disabilities who lack support etc...). Can we add that Trusts should therefore not reject referrals: (1) if a FIT result could not be appended with the referral and (2) if there is a strong clinical suspicion from the GP that the patient may have a	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that, for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of

Comment number	Name and organisation	Section number	Comment	NICE Response
			colorectal cancer despite a FIT score of <10 (as reflected in section 3.15 of this document)?	faeces… 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). How secondary care handle referrals is outside the scope of the assessment, but it was noted in section 3.20 that experts stated that secondary care centres should be able to accept referrals without a positive FIT result.
100 part 2	NHSE		2. We recommend that whilst reviewing the age thresholds for various symptoms that a recommendation is made that FIT should be used primarily in those over 40. At the moment the guidance reads that anyone under 50 with rectal bleeding and symptoms should have a FIT which leaves the age threshold for FIT fully open. This could risk a number of low-risk referrals coming through to secondary care 3. We recommend that NICE aligns with BSG for abdominal masses and suggest the following 'patients with signs of an abdominal mass should be referred urgently, however a FIT should be requested simultaneously in primary care to inform the subsequent investigation'. 4. There is a recommendation 'Referral to secondary care should not be delayed in the absence of a FIT result if there is a clinical concern.' We would recommend adjusting this to 'Referral to secondary care should not be delayed in the absence of a FIT result if there is a clinical concern. The referring clinician should consider whether a referral on an alternative pathway, for example a non-specific- symptoms pathway is more appropriate.	Thank you for your comment. The committee considered evidence on factors such as age that could influence the threshold that should be used to guide referral or affect the diagnostic accuracy of the test. However, there was limited evidence and the committee was unable to make recommendations that FIT should be used differently based on age. Research recommendations were made to evaluate the diagnostic accuracy of FIT in people under 40 where the prevalence of colorectal cancer may be lower (see section 3.7 and 4.3). The committee agreed that a referral on a suspected cancer pathway was more likely for people with an abdominal mass, but that since it is not a specific symptom of colorectal cancer, a FIT result would still be useful to make sure that the person has the most appropriate investigation. So, abdominal mass was not specifically identified as a bypass symptom but was referred to as a possible reason to refer without waiting for a FIT result in recommendation 1.3, which now reads: "for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… referral to an appropriate secondary care pathway should not be delayed if there is strong clinical concern of

Comment number	Name and organisation	Section number	Comment	NICE Response
				cancer because of ongoing unexplained symptoms (for example, abdominal mass)". A colorectal cancer pathway is not specified here because other pathways may be more appropriate depending on the results of FIT and other tests. For more detail see section 3.3 and 3.20 in the guidance.

THEME: Safety netting

Comment number	Name and organisation	Section number	Comment	NICE Response
27	Web comment Calderdale Cares Partnership	3.14	Please can we be clear about when a repeat FIT test would be offered if the first one was negative? 4 weeks seems like a reasonably practicable timescale.	Thank you for your comment. The committee commented that no evidence was presented on the relative effectiveness of different forms of safety netting, so no specific recommendations could be made. But, the committee discussed the different options for safety netting that are available. Please see sections 3.12 and 3.19 of the guidance for more detail.
48 part 4	Web comment (ACPGBI)		1.4 ACPGBI support this recommendation and would suggest including reference to sources of established Safety Netting Pathways referred to in the main guideline document.	Thank you for your comment. Reference to existing advice can be found in section 3.19 of the guidance.
67	Web comment Humber and North Yorkshire Cancer Alliance	1.4	Discussions with primary care clinicians indicates that they feel that this recommendation is vague and not reflective of primary care system pressure and the resources needed to undertake these safety netting processes.	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

Comment number	Name and organisation	Section number	Comment	NICE Response
71	Web comment Humber and North Yorkshire Cancer Alliance	3.14	Considering the discussion on the effectiveness of dual FIT (3.7) an inclusion in the guidance on the the use of a repeat FIT as a safety-netting measure would seem important to avoid confusion.	Thank you for your comment. The committee commented that no evidence was presented on the relative effectiveness of different forms of safety netting, so no specific recommendations could be made. But, the committee discussed the different options for safety netting that are available. Please see sections 3.12 and 3.19 of the guidance for more detail.
72	Web comment Humber and North Yorkshire Cancer Alliance	3.14	It could be useful to emphasis the role of non-specific symptom pathways in the investigation of FIT-negative symptomatic patients as a key alternative referral route for patients that GPs have on-going concerns for.	Thank you for your comment. Recommendation 1.3 now reads: “for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)”. A colorectal cancer pathway is not specified here because other pathways may be more appropriate depending on the results of FIT and other tests, and the non-specific symptoms pathway has been highlighted in the committee considerations. For more detail see section 3.3 and 3.20 in the guidance.
80	Web comment Cancer Research UK	1.4	The evidence base largely suggests that most people with CRC and a FIT ‘negative’ (< 10 µg/g) result have anaemia and/or weight loss – therefore, it may be useful for health professionals to be aware of this and consider referral for people with anaemia if there is ongoing clinical concern, regardless of a ‘negative’ FIT. Similar trends have also been evidenced for replicate/repeat FIT. This relates to the evidence reported by NICE of FIT having lower sensitivity for people with anaemia compared to no anaemia. Additionally, the evidence on extra-colonic cancer risk in people with a ‘negative’ FIT and symptoms within the current NG12 guidance should be considered. Previous research has found that all-cancer risk remains high in these patients (at 6%) . (7-17) There is evidence to suggest that GPs require further information and support to safety net FIT ‘negative’ patients confidently. In a Cancer Research UK GP survey	Thank you for your comment. The committee noted that there the evidence is not clear on how iron-deficiency anaemia affects the performance of FIT. It concluded that FIT was still appropriate for people with iron-deficiency anaemia (see sections 3.3 and 3.7 in the guidance). Recommendation 1.3 now reads: “for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)”. A

Comment number	Name and organisation	Section number	Comment	NICE Response
			conducted in February 2023, 39% of GPs said they were 'Very confident' managing and safety netting 'negative' patients with ongoing symptoms . Whilst reported confidence was fairly high, there was still a significant proportion (60%) of UK GPs who reportedly lacked confidence to some degree. Furthermore, 63% and 43% of UK GPs said that local FIT pathway guidance and national FIT pathway guidance would increase their confidence managing and supporting FIT negative patients with persistent, unexplained symptoms. As the use of symptomatic FIT becomes more embedded in practice, the evidence demonstrating which safety netting practices are the most effective in which circumstances/for which patients will become more robust. At this stage, we recommend considering the inclusion of effective examples of safety netting practice to encourage and inform the implementation of robust safety netting. (18) This recommendation should be strengthened by the considering the inclusion of information on anaemia and extra-colonic cancer risk. The use of Clinical Decision Support (CDS) tools could also be considered to help health professionals assess risk in FIT 'negative'. There could be additional detail on the safety netting steps that health professionals can take. On the challenge of non-responders, the Cancer Research UK July 2022 GP Omnibus asked GPs if their practice used any methods to follow up with patients who did not complete or return their FIT kit. 19% of GP respondents said they did not know if there was a mechanism in place to follow up with patients and 22% said that there wasn't one. Set protocols could support safety netting practices for non-responders. As discussed in our answer to the question has all of the relevant evidence been taken into account, the February 2023 GP Omnibus survey results indicated an appetite amongst GPs for guidance to support with the management of symptomatic patients who took the test but received a negative result. Between 30-40% of GP respondents also said the following resources would help to increase their confidence: a summary of the latest evidence on optimal FIT use for suspected colorectal cancer; an infographic of the referral pathway for suspected colorectal cancer patients; and digital information that can be sent to patients showing how to complete a FIT and why it is important to do so. The most popular channels to receive safety netting support from in the February 2023 survey were educational resources (36%),	colorectal cancer pathway is not specified here because other pathways may be more appropriate depending on the results of FIT and other tests. Reference to existing advice on safety netting can be found in section 3.19 of the guidance. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

Comment number	Name and organisation	Section number	Comment	NICE Response
			newsletters (23%) and local health systems support (23%). (19,20) (7) Farrugia A, Widlak M, Evans C, et al. Faecal immunochemical testing (FIT) in symptomatic patients: what are we missing? Frontline Gastroenterology 2020;11:28-33. (8) Cunin, Laila, Aftab Alam Khan, Maria Ibrahim, Artemisia Lango, Michail Klimovskij, and Raj Harshen. "Fit Negative Cancers: A Right-Sided Problem? Implications for Screening and Whether Iron Deficiency Anaemia Has a Role to Play." The Surgeon 19, no. 1 (2021/02/01/ 2021): 27-32. (9) Chapman C, Bunce J, Oliver S, Ng O, Tangri A, Rogers R, Logan RF, Humes DJ, 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 Jan 28;3(3):395-402. doi: 10.1002/bjs5.50131. (10) Mowat C, Digby J, Strachan JA, et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. BMJ Open Gastroenterology 2019;6:e000293. doi: 10.1136/bmjgast-2019-000293 (11) J A Bailey and others, Faecal immunochemical testing and blood tests for prioritization of urgent colorectal cancer referrals in symptomatic patients: a 2-year evaluation, BJS Open, Volume 5, Issue 2, March 2021, zraa056, https://doi.org/10.1093/bjsopen/zraa056 (12) Farkas NG, Fraser CG, Maclean W, Jourdan I, Rockall T, Benton SC. Replicate and repeat faecal immunochemical tests in symptomatic patients: A systematic review. Ann Clin Biochem. 2022 May 5:45632221096036. doi: 10.1177/00045632221096036. (13) Hunt N, Rao C, Logan R, et al. A cohort study of duplicate faecal immunochemical testing in patients at risk of colorectal cancer from North-West England. BMJ Open 2022;12:e059940. doi: 10.1136/bmjopen-2021-059940 (14) Farkas NG, O'Brien J, Whyte M, Jourdan I, Rockall T, Benton SC. An observational study of replicate faecal immunochemical tests in the urgently referred symptomatic cohort. Annals of Clinical Biochemistry. 2023;0(0). doi:10.1177/00045632231163425 (15) A D Gerrard and others, Double faecal immunochemical testing in patients with symptoms suspicious of colorectal cancer, British Journal of Surgery, Volume 110, Issue 4, April 2023, Pages 471–480, https://doi.org/10.1093/bjs/znad016 (16) Johnstone, MS, MacLeod, C, Digby, J, Al-Azzawi, Y, Pang, G, Watson, AJM, Prevalence of repeat faecal immunochemical testing in symptomatic patients attending primary care. Colorectal Dis. 2022; 24: 1498– 1504.	

Comment number	Name and organisation	Section number	Comment	NICE Response
			https://doi.org/10.1111/codi.16240 (17) Faux JW, Cock K, Bromley R, Feldman M. Colorectal two-week wait service and quantitative FIT: it's not just about colon cancer. Ann R Coll Surg Engl. 2022 Apr;104(4):257-260. doi: 10.1308/rcsann.2021.0184. (18) Cancer Research UK GP Omnibus survey (2023) Unpublished findings. Data collected by medeConnect who interview 1000 regionally representative UK GPs online. medeConnect is a division of Doctors.net.uk (19) Cancer Research UK GP Omnibus survey (2022) Unpublished findings. Data collected by medeConnect who interview 1000 regionally representative UK GPs online. medeConnect is a division of Doctors.net.uk' (20) Cancer Research UK GP Omnibus survey (2023) Unpublished findings. Data collected by medeConnect who interview 1000 regionally representative UK GPs online. medeConnect is a division of Doctors.net.uk Please note, we'd be happy to discuss the results of our omnibus surveys and the CAM, cited above, if helpful.	
98	Web comment (organisation not stated)	1.4	Can we please specify what we mean by this by providing some examples e.g. as outlined in section 3.14? Also, GPs should consider other cancer types (beyond colorectal cancer) when there are concerning symptoms and the FIT is <10.	Thank you for your comment. The committee commented that no evidence was presented on the relative effectiveness of different forms of safety netting, so no specific recommendations could be made. Reference to existing advice on safety netting can be found in section 3.19 of the guidance. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
100 part 5	NHSE		5. Where there is a recommendation that safety netting processes should be in place can we recommend further support, we would recommend what was included in the NHSE communication: o Providing the patient with clear information about who to contact if they develop new symptoms or if their existing symptoms worsen. o Using advice and guidance via eRS to guide management of patients with persistent or troublesome symptoms. o Offering a second FIT test if ongoing clinical concerns remain. o Referral to a non-specific-symptoms urgent cancer pathway, if appropriate and there are ongoing concerns about possible cancer o Management of FIT negative patients in an outpatient setting following referral on a non-urgent pathway.	Thank you for your comment. The NHSE communication is referred to in section 3.19 of the guidance. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

THEME: Further clarifications

Comment number	Name and organisation	Section number	Comment	NICE Response
5	Web comment (organisation not stated)	1.1 'excluding those with rectal mass'	This important paragraph component is located within bracket & therefore easy to miss. It would make it clearer if only reference to previous recommendations was included within the bracket i.e. '... guide referral for adults with signs or symptoms of colorectal cancer, excluding those with a rectal mass (as outlined in ....)'	Thank you for your comment. Recommendation 1.1 has been adapted to specifically list the symptoms that FIT is recommended for by this piece of guidance. Guidance on referral for people with rectal mass will be outlined in NG12, but it is also specified in 1.1 and in the rationale that people with certain symptoms of colorectal or anal cancer (rectal or anal mass, or anal ulceration) do not need to be offered FIT before referral.
8 part 3	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	1.3	In 1.3, the term 'clinical concern' is too broad and goes against recent study and current guidance - this sentence will cause unnecessary confusion amongst providers/services	Thank you for your comment. The wording of recommendation 1.3 now reads: "for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)".
9	Web comment - Lancashire & South Cumbria Cancer Alliance - LSCCA	2.3	Please define 'high risk' - see my comments at 1.3 re defining 'red flag symptoms'	Thank you for your comment. As NG12 will be updated at the same time as this guidance is published, the previous definitions of 'low' and 'high' risk symptoms have been outlined in section 2.3 of the guidance.
10	Web comment - Lancashire & South Cumbria Cancer Alliance – LSCCA	2.5	I agree this should be referenced - but this seems to conflict with section 1.3 of this document.	Thank you for your comment. Recommendation 1.3 now reads: "for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)".
13	Web comment - Lancashire & South Cumbria	3.15	Happy with this comment as it offers specificity - but I feel that reflecting this in 1.3 in recommendations will cause unnecessary confusion for providers.	Thank you for your comment. Committee felt that recommendation 1.3 was important to ensure that referrals without FIT results were not

Comment number	Name and organisation	Section number	Comment	NICE Response
	Cancer Alliance - LSCCA			refused by secondary care centres. Recommendation 1.3 now reads: "for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)".
18	BSG	1.2	1.2 The BSG support this recommendation that FIT be used in all adults with signs or symptoms of suspected CRC. It would be important to clarify what is meant when referring to symptoms in previous guidance and this may be misinterpreted by clinicians as suggesting amore selective approach. Although there has been some additional relevant evidence produced since the BSG/ACP guideline in 2022 this is not yet substantial - albeit may contribute to evolution of the recommendations in future iterations, for example with regard to repeat/duplicate testing. Similarly evidence since 2022 about the effect of population factors, modelling, and subgroups has not demonstrated the value of using different approaches accordingly or discriminating between populations. Therefore the BSG support the approach of using FIT is adults with signs or symptoms of suspected CRC. It is also specifically helpful that younger adults have not been excluded as otherwise this would results in loss of access to urgent investigation in younger people with symptoms. FIT provides primary care with a method of selecting people with signs or symptoms with an objective method of assessing those at highest risk of CRC, including younger patients and other populations.	Thank you for your comment. The previous definitions of 'low' and 'high' risk symptoms have been outlined in section 2.3 of the guidance. Recommendation 1.1 has been adapted to specifically list the symptoms that FIT is recommended for by this piece of guidance.
19	BSG	1.3	1.3 The BSG support the recommendation that FIT should not be a sole arbiter of referral. However perhaps the committee could clarify what is meant by 'clinical concern' as otherwise this may lead to ad hoc variation in practice. It may be helpful to state that those with FIT < 10 may also be managed in primary care without referral.	Thank you for your comment. Recommendation 1.3 now reads: "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

Comment number	Name and organisation	Section number	Comment	NICE Response
				cancer because of ongoing unexplained symptoms (for example, abdominal mass)". Section 3.19 of the guidance includes that management in primary care is an option for safety netting.

Comment number	Name and organisation	Section number	Comment	NICE Response
39	Web comment (organisation not stated)	2.3 offering FIT to people presenting to primary care with 'low risk' symptoms of colorectal cancer	I would suggest that symptoms are mentioned as this document and DG30 discuss the use of FIT in primary care with low risk, but with symptoms. Low risk could be interpreted as no symptoms, but patient request, FIT would be inappropriate outside the screening programme in asymptomatic patients	Thank you for your comment. Recommendation 1.1 has been adapted to specifically list the symptoms that FIT is recommended for by this piece of guidance. People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme.
40	Web comment (organisation not stated)	2.18 'low risk' symptoms	this is a good term "low risk Symptoms" and preferable to "low risk"	Thank you for your comment. Recommendation 1.1 has been adapted to specifically list the symptoms that FIT is recommended for by this piece of guidance. The terms 'low risk symptoms' and 'high risk symptoms' are not used in the recommendations as the committee have recommended FIT for all symptoms suggestive of colorectal cancer except for specific bypass symptoms (rectal or anal mass, anal ulceration). People without symptoms are not in the scope of the assessment, but may be covered by the bowel cancer screening programme.
48 part 3	Web comment (ACPGBI)		1.3 ACPGBI support this recommendation but would suggest that the term "clinical concern" would benefit from further clarification given that this guidance may be used in Primary Care by non-specialist clinicians. We would suggest that the benefit of the use of FIT to identify patients who are at increased risk of Colorectal Cancer of Urgent Referral should be emphasised while confirming that where there is a high index of clinical suspicion urgent referral can still be considered in the presence of a FIT result <10mcgHb/g or absence of a completed FIT test, particularly in those with persistent symptoms.	Thank you for your comment. The wording of recommendation 1.3 now reads: "for people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces… 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)".

Comment number	Name and organisation	Section number	Comment	NICE Response
50	Bowel Cancer UK		**Referral on suspected cancer pathway: data** The data used to indicate the number of people with suspected gastrointestinal cancer who were seen under a suspected cancer pathway is from 2020-2021 and therefore outdated. This is particularly important given that the data represents a period during the breakout of the COVID-19 pandemic with a significant reduction in urgent suspected cancer referrals, with around 330,000 fewer referrals in England from April 2020 – March 2021. Health service data varies significantly from year to year, so it is vital that this is updated to data from 2023 to provide a more accurate representation of current cancer waiting times, especially as there was a significant increase in referrals following Dame Deborah James' diagnosis, awareness work, and passing last year. The data used from 2020-2021 states that 88.9% of people referred for suspected lower gastrointestinal cancer were seen within two weeks. This however does not provide a true and accurate picture of when patients received a confirmation of diagnosis or colorectal cancer or rule out, and therefore we would recommend using the Faster Diagnosis Standard. This decreased by almost 6%, as only 83% of people were seen by a specialist within two weeks of an urgent referral for suspected lower gastrointestinal cancer, and 17% of patients waited longer than this target (NHS England Cancer Waiting Times, May 2023). The data used from 2020-2021 also states that only 50.6% of patients referred urgently under a suspected cancer pathway received treatment within 62 days, compared with an operational standard of 85%. Only 38% of people treated for lower gastrointestinal cancers received first definitive treatment within 62 days of being urgently referred for suspected cancer (NHS England Cancer Waiting Times, May 2023). Given these figures, we believe that this evaluation is of some urgency. Moreover, as the two-week wait standard to see a specialist will soon be scrapped, the faster diagnosis standard could paint a more accurate picture of diagnostic waiting times. In May 2023, for all routes, 53% of people were told by a specialist if they had cancer, or if was cancer was definitively excluded within 28 days of an urgent referral for lower GI cancer (NHS England Cancer Waiting Times, May 2023).	Thank you for your comment. The external assessment group commented that the 2020-2021 data referred to in the comment was not directly used in the model, and was used only for context. NICE will produce a resource impact tool which will help commissioning groups evaluate the likely impact of implementing FIT in their centres.

Comment number	Name and organisation	Section number	Comment	NICE Response
54	Web comment (organisation not stated)	1.1 excluding those with rectal mass).	Further clarify on why patients with rectal mass are excluded would be beneficial.	Thank you for your comment. Rectal mass was identified as a bypass symptom during scoping and so people with rectal mass are outside the scope of this assessment. This has been clarified in recommendation 1.1. Guidance on management of people with rectal mass will be outlined in NG12. For more detail please see section 3.3 in the guidance.
55	Web comment (organisation n ot stated)	1.3 Referral to secondary care should not be delayed in the absence of a FIT result if there is clinical concern.	It would be useful to have a clearer definition of "clinical concern". Is this limited to high-risk/'red-flag' symptoms such as rectal bleeding/abdo mass or is this any gut feeling of suspected colorectal cancer? If the symptoms are not 'red-flag', would patients not be more appropriately referred to the NSS pathway?	Thank you for your comment. The wording of recommendation 1.3 has been updated to state that 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). A colorectal cancer pathway is not specified here because other pathways may be more appropriate depending on the results of FIT and other tests.

THEME: Implementation

Comment number	Name and organisation	Section number	Comment	NICE Response
2	Web comment (organisation not stated)	1.5	Is there any opportunity to include that faecal matter on gloved finger could be used given that patients will need DRE so the test could be fulfilled at the same time	Thank you for your comment. Specific guidance on sample collection is outside the scope of this assessment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
4	Web comment (organisation not stated)	1.4	I don't think the perceived 'burden' on primary care can be underestimated here. Getting practices to engage is incredibly difficult as they see this as secondary care work being 'dumped' and creating additional work which is not directly contracted	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

Comment number	Name and organisation	Section number	Comment	NICE Response
			though nobody would disagree that using FIT is far superior than exposing patients to unnecessary colonoscopy	
22	BSG	1.6	1.6 The BSG support this research recommendation. With regard to the implementation and research sections of the NICE guideline we would like to signpost the supplement produced within the BSG/ACP guideline which may be helpful (supplement 3) https://gut.bmj.com/content/71/10/1939#supplementary-materials	Thank you for your comment.
23	BSG	1.7	1.7 The BSG support this research recommendation. With regard to the implementation and research sections of the NICE guideline we would like to signpost the supplement produced within the BSG/ACP guideline which may be helpful (supplement 3) https://gut.bmj.com/content/71/10/1939#supplementary-materials	Thank you for your comment.
45	Web comment (organisation not stated)	3.12 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	i support the threshold of 10 microgrammes of Hb per gram of faeces for referral. We increasingly see GPs requesting FIT in asymptomatic patients. Periodically patients in this group have a positive FIT (but less than 25). This should not be used as an argument to raise the threshold; we need to emphasis that the patient must have low risk symptoms before getting a GP FIT test)and keep the threshold at 10). I would suggest that the actual result (microgramme Hb per gram of faeces is reported, which will allow further research/audit. I would support harmonisation of reporting units and decimal points. I would suggest that a set of agreed comments are used for NEG and POS results	Thank you for your comment. Specific guidance on reporting procedures is outside the scope of this guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
		higher thresholds were more uncertain (see section 3.10). 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).		
46	Web comment (organisation not stated)	3.11 Choice of threshold	whilst i support the threshold of 10, we know that there is measurement uncertainty between methods, which can lead to unwarranted variation in results, bias etc. There are other methods than NICE suggest a cut-off (PSA, CA125 etc) where the laboratory performances are so variable that having a single threshold across different methods is unhelpful. I would suggest that performance criteria be investigated to ensure that methods/laboratories are performing acceptably. UKNEQAS have this data and if an threshold of 10 is being recommended then we need to ensure that the laboratory/method meets the performance criteria so that the threshold of 10 remains relevant. NICE/ACB/UKNEQAS would be able to assist	Thank you for your comment. Specific guidance on quality assurance is outside the scope of this guidance.
48 parts 4 to 6	Web comment (ACPGBI)		1.4 ACPGBI support this recommendation and would suggest including reference to sources of established Safety Netting Pathways referred to in the main guideline document. 1.5 ACPGBI support this recommendation and provide more detailed guidance in the ACPGBI-BSG Guideline to aid establishment of processes to support this aspect of FIT testing compliance.	Thank you for your comment. Reference to existing advice on safety netting can be found in section 3.19 of the guidance. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

Comment number	Name and organisation	Section number	Comment	NICE Response
			1.6 ACPGBI supports this recommendation. There are still many aspects of the used of Quantitative FIT testing which are not defined. ACPGBI-BSG have published supplementary Research and Implementation Sections with this Guideline (https://gut.bmj.com/71/10/1939#supplementary-materials) which could be referenced. Reference: 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). Monahan KJ, et al. Gut 2022;71:1939–1962. doi:10.1136/gutjnl-2022-327985	
49	Bowel Cancer UK		**Purpose of the medical technology** As an organisation with a strong emphasis on early diagnosis, we welcome the new draft guidance on the use of quantitative FIT to guide colorectal cancer (CRC) pathway referral in primary care. The use of FIT for all symptomatic patients could allow for more accurate triaging for suspected CRC patients, so those most likely to have CRC can be prioritised effectively. The use of FIT can effectively indicate which patients are less likely to have CRC, meaning that those who do not require a colonoscopy can be monitored in primary care without the need for a referral or to undergo this invasive procedure. Referral delays of 3 months (for patients with red flag symptoms of CRC) are associated with a significantly worse prognosis than those referred within 2 weeks, and so FIT is essential for identifying and referring high-risk patients earlier (BJGP, 2022). A quantitative study used within the guidelines on FIT, in patients with signs and symptoms of CRC, from the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG) suggests that 90.2% of people found the kits straightforward to use, 76.3% disagreed that the tests were unhygienic and 78.1% preferred FIT to colonoscopy. Avoiding colonoscopy, where possible, is preferential for patients, and therefore the use of FIT more widely for symptomatic patients will help to ease colonoscopy capacity issues, enable urgent access to those at high-risk of CRC and improve overall patient experience.	Thank you for your comment.
68	Web comment	1.7 There is also concern that using a higher threshold would reduce	This is an important factor that is compounded by confused understanding of the level justifications for FIT used within the bowel screening programme and FIT used for symptomatic patients. Both GPs and colorectal physicians have expressed confusion over the relative meaning of positive/negative results for a FIT screening test and a	Thank you for your comment. Recommendation 1.1 now specifically states that FIT should be offered even if the person has previously had a

Comment number	Name and organisation	Section number	Comment	NICE Response
	Humber and North Yorkshire Cancer Alliance	physician confidence in the test results (because more people with cancer may be missed) and so affect clinical decision making.	symptomatic FIT test. This is as big a challenge to clinician confidence as the level itself.	negative FIT result through the NHS bowel cancer screening programme.
83	Web comment Cancer Research UK	5	Cancer Research UK provides the following resources for health professional to support the successful completion and return of FIT symptomatic kits: • The patient-facing guide, 'Tips for collecting your poo' (link https://www.cancerresearchuk.org/sites/default/files/943_fit_symptomatic_update_landscape_2.pdf) • 'Symptoms of bowel cancer' patient-facing video (link https://www.youtube.com/watch?v=egAkVFSps_c) • 'FIT Symptomatic' web page on Cancer Research UK's Health Professional Hub (link https://www.cancerresearchuk.org/health-professional/diagnosis/primary-care/primary-care-investigations/fit-symptomatic) • 'Screening vs. Symptomatic FIT infographic' (link https://www.cancerresearchuk.org/sites/default/files/england_key_differences_infographic_2021.pdf). The graphic supports GPs to explain to patients the different uses of FIT and the importance of completing a symptomatic test, even if they have recently completed one for screening. • 'Supporting the recognition, referral and management of suspected bowel cancer' two-page guide (link https://www.cancerresearchuk.org/sites/default/files/bowel_cancer_guide_april_2023.pdf). It provides an overview of the guidance and resources available to support GPs with suspected bowel cancer cases.	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
87	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	2.8	2.8 Member A;.The Table of data provided by manufacturers shows some interesting use of significant figures after the decimal point. Bearing in mind the imprecision of the assays and the heterogeneity of the measurand, I think that it is vital that the guidance considers the reporting of data on f-Hb. I suspect that there is considerable variation	Thank you for your comment. Specific guidance on reporting procedures is outside the scope of this guidance.

Comment number	Name and organisation	Section number	Comment	NICE Response
			in reporting formats across the UK. I strongly suggest that the following is reviewed in detail and similar recommendations made in DAB50: doi: 10.1515/cclm-2018-0464.	
91 part 4	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.12	I suggest that the result (ug Hb/g Faeces) is reported as well as POS/NEG to allow for research/audit I raise concern about the laboratory/manufacturer performance if a single magic number is used. I suggest that the work with the ACB and EQA providers to develop performance criteria. We cannot have significant biases with the same target (also true for CA125, PSA etc)	Thank you for your comment. Specific guidance on reporting procedures is outside the scope of this guidance.
93 part 2	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	5	Members B & C;. Harmonisation of Reporting. Need for consensus suggested on the following; number of decimal places reported, how to report above the upper limit (i.e > or dilution to get absolute value). Consensus highly recommended for interpretative comments as this will affect the next steps in the patient pathway and may be currently as per local practice.	Thank you for your comment. Specific guidance on reporting procedures is outside the scope of this guidance.
102	Red Trouser Day		I think extending the use of FIT Tests is a good idea in general, it is certainly better than some of the GP referrals I have heard about. I would also suggest that better education for GP's when examining a patient for suspected bowel cancer would also be very useful. I was fortunate in that my GP examined my rectum and found a polyp. We are working with some senior consultants and GP's looking at ways that this examination can be improved with a simulator. If the GP could be confident in this process, the delay of a FIT test would not be needed and they could move straight to an informed referral for colonoscopy. I have heard many patients cite their GP as not believing they could have bowel cancer so started putting people on laxatives and things like that. GP education and junior doctor education at A&E is critical to reduce the late staging.	Thank you for your comment. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice. Specific guidance on examination of people with symptoms in addition to offering FIT is outside the scope of this assessment.

THEME: Comments out of scope

Comment number	Name and organisation	Section number	Comment	NICE Response
28	Web comment Calderdale Cares Partnership	3.15	In order to avoid unnecessary colonoscopies, I think we should be encouraging secondary care to perform a FIT test on patients that have been referred without a FIT test as this may help determine who requires an urgent colonoscopy. We know that patients are sometimes more likely to comply with this request if it comes via secondary, rather than primary, care.	Thank you for your comment. Use of FIT in secondary care is outside of the scope of this assessment.
86	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	2.2	2.2 Member A;.Is there a role for colon capsule endoscopy in this context - doi: 10.1111/codi.16029?	Thank you for your comment. Colon capsule endoscopy is currently being evaluated in a separate NICE assessment (please see GID-DG10083)
91 part 2	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)	3.12	Finally, I would put it to the group that a very important consideration has been omitted. That is the vital role that a full blood count has in the diagnostic process along with the f-Hb result. There are several peer-revied publications concerning this. Even if this were only documented as suggested above for 3.4 as an additional vital investigation.	Thank you for your comment. This assessment is only looking at the use of FIT to guide referral. Combining FIT with other measurements such as blood count is being evaluated in the COLOFIT study which is the topic of another NICE assessment (see GID-HTE10011).

THEME: Comments in support or no comments

Comment number	Name and organisation	Section number	Comment	NICE Response
3	Web comment (organisation not stated)	1.3	This is a really positive addition	Thank you for your comment.
16	BSG		The BSG broadly support the recommendation made by the NICE committee. They are consistent with the guidelines produced by BSG/ACP in 2022, and therefore will support a consistent approach and implementation across primary and secondary care. It may be helpful for clinicians for NICE to actively signpost to the BSG/ACP guidelines as they contain more detail about methods to implement, and approaches to specific situations e.g. where patients have not returned a FIT.	Thank you for your comment.

Comment number	Name and organisation	Section number	Comment	NICE Response
20	BSG	1.4	1.4 The BSG support this recommendation.	Thank you for your comment.
21	BSG	1.5	1.5 The BSG support this recommendation. The BSG/ACP guidelines have included recs “Advice for clinicians where patients have not returned a FIT test” which could perhaps be signposted	Thank you for your comment.
48 parts 1 and 2	Web comment (ACPGBI)		Response of the Association of Coloproctology of Great Britain & Ireland (ACPGBI) to NICE Draft Guidance for Quantitative faecal immunological testing to guide colorectal cancer pathway referral in primary care. [redacted] on behalf of the Executive Committee of the ACPGBI The ACPGBI has reviewed with interest these recommendations from NICE and note that they confirm the economic aspects of Quantitative FIT testing (QFIT). The recommendations further support the implementation of the use of QFIT in patients with symptoms suggestive of colorectal cancer following the Joint ACPGBI- BSG Guidelines on the Use of Symptomatic FIT testing (2022). We provide our detailed response to each of the recommendations below. The evidence supports the safe use of QFIT to identify a higher risk group of patients with bowel symptoms who should be urgently referred along a Suspected Cancer Pathway. Clinical suspicion remains important where symptoms are persistent in those with FIT tests below threshold but the majority of patient can be managed safely in primary care. We would suggest that the benefit of this approach could be further emphasised in these recommendations. Reference to defined processes for Safety Netting and education of those adopting use of QFIT will further support this safe approach. Recommendations: 1.1 ACPGBI supports this recommendation based on the evidence provided. 1.2 ACPGBI supports this recommendation for the use of FIT at a threshold of 10 mcg Hb/g to triage patients with symptoms of suspected colorectal cancer into a higher risk group for referral on a suspected cancer pathway. The reference to the previous NICE NG 12 Guideline is noted which includes use of age as a discriminating factor. There is evidence to support use of symptomatic FIT testing below the age of 50 years and we would suggest that this is emphasised, particularly given the increasing incidence of Colorectal Cancer in the sub 50 year old population.	Thank you for your comment. The committee did not make any recommendations that FIT should be used differently according to age, although the symptoms that are an indication for FIT described in section 1.1 do still contain reference to age as these were defined by the previous 'low’ and ‘high’ risk populations outlined in DG30 and NG12. A research recommendation was made for people under 40 (see section 4.3).

Comment number	Name and organisation	Section number	Comment	NICE Response
76 part 1	Web comment Cancer Research UK	1.1	The NICE review accounts for evidence up to June 2023. Since then, additional evidence has been published which supports the use of FIT in primary care to help guide referral for adults with signs or symptoms of colorectal cancer, including those under 50 years old (1). We welcome alignment to the BSG guidance published last year. Any discrepancies between the two sets of guidance should be acknowledged and explained to support health professionals and avoid confusion. 1) Tibbs RE, Benton SC. A service evaluation of the use of faecal immunochemical tests in symptomatic patients aged under 50 years presenting to primary care. Annals of Clinical Biochemistry. 2023;0(ja). doi:10.1177/00045632231189386	Thank you for your comment. The external assessment group noted that their searches were conducted in December 2022, though additional evidence provided by clinical advisors was included if it was identified prior to running the synthesis analysis (April/May 2023). Data was not systematically searched for between December 2022 and June 2023. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.
78	Web comment Cancer Research UK	1.2	Please see response to recommendation 1.1	Thank you for your comment.
79	Web comment Cancer Research UK	1.3	No comments	Thank you for your comment.
84 part 1	Web comment ACB - Scientific Affairs and Clinical Practice (SACP)		ACB Member's Submission on DAB 50 Member A; [redacted] Member B; Member C; Member D; Member E; Opening Comments Opening Comments Member B; Welcomes the document. Member A; Supports the recommendation (in particular of HM-JACKarc and OC-Sensor as the FIT systems and the use of the 10 µg Hb/g faeces as these are evidence-based.	Thank you for your comment.

Comment number	Name and organisation	Section number	Comment	NICE Response
101	NHSE Genomics Unit		We have reviewed the documents associated with this application. The testing within this appraisal sits outside of the scope of testing delivered by the Genomic Medicine Service. As such this is not within our remit and we are not in a position to provide comments from the Genomics Unit.	Thank you for your comment.

Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence – Diagnostics Assessment Report Guide

Addendum number 3: Quantitative faecal immunochemical tests to guide colorectal cancer pathway referral in primary care, response to ACD

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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TABLES

FIGURES

1 Introduction

In response to additional relevant data (one study, Jordaan et al 2023)[1] provided by Sysmex/Sentinel during the assessment consultation period, the EAG has prepared this addendum, which includes the following:

1. Introduction
2. Rational for the new analyses
3. New FOB Gold syntheses
   - 3.1. New primary analysis for FOB Gold.
   - 3.2. New sensitivity analysis for FOB Gold.
   - 3.3 Summary of updated synthesis results
   - 3.4. A brief summary of uptake, failure and repeat test data for FOB Gold, to include the new FOB Gold study.
4. All tests together synthesis updated with changes to FOB Gold evidence base.
   - 4.1 Statistical synthesis of all tests – primary analysis
   - 4.2 Statistical synthesis of all tests – sensitivity analysis
   - 4.3 Summary of updated results – all tests
   - 4.4 Summary of meta-analysis of diagnostic test accuracy
5. Cost effectiveness results for FOB gold
   - 5.1, updated FOB Gold analyses, using low intensity safety netting.
   - 5.2, updated FOB Gold analyses, using high intensity safety netting.
6. Conclusions
7. Appendix A. An additional sensitivity analysis where one study is removed due to low numbers and possible patient spectrum issues.

This addendum should be read in conjunction with the original assessment report.[2]

2 Rationale for the new analyses

In their comments on the ACD, the company provided three new studies.[1, 3, 4] One met the inclusion criteria for the review.[1] One study[3] had already been considered by the EAG in its original report, but excluded because the method used to obtain the faecal sample was digital rectal examination, which clinical advisors to the EAG stated is extremely rare in primary care. The third study[4] contained insufficient data to extract TP, TN, FP and FN or sensitivity and specificity and could therefore not be included in the review.

The committee made research recommendations for FOB Gold. The systematic review criteria (see Section 4.1.1 of the EAG report) allowed for the inclusion criteria to be relaxed if little or no data were available that met the inclusion criteria. In addition, since the company again highlighted the evidence they had submitted previously, the EAG has revisited the studies submitted by the company in their 2022 submission to NICE.[5-14] During this review, the EAG has identified two[9, 12] that were excluded because patients were recruited from both primary and secondary care referrals,[9] or for which it was unclear if they were recruited from both settings.[12] There was a potential cross-over (based on recruitment dates, the location was not reported for one study but authors were from the same hospital in both studies) between these two studies. The EAG had excluded these studies as it was concerned that recruitments from secondary care may represent a population with different severity or type of symptoms, and higher prevalence of disease. A different patient spectrum may alter sensitivity and specificity estimates. During the revisiting of studies, the EAG also noted that one of the FOB Gold studies included in the original EAG analysis was not clear about whether patients were referred to colonoscopy from primary and/or secondary care (Schwettmann *et al.* 2022),[14] and should have been excluded for consistency with the decisions on the other papers. All other studies submitted by the company were excluded in accordance with the review selection criteria (see EAG response to consultation comment 29).[15]

The EAG did not identify any studies relating to the IDK tests or NS-Prime (where the evidence base was small) that had been excluded for similar reasons. One study[16] was also excluded for QuikRead go for similar reasons, but this was a small study (13 CRC events, 242 patients analysed). The original evidence base comprised one study (14 CRC events, 553 patients analysed).[17] The results of each study are presented in the EAG report,[2] Tables 17 and 11 respectively. Given the limited time available, the EAG have not updated this analysis.

This addendum therefore provides two new analyses:

- New primary analysis for FOB Gold (Section 2.1). This updates the existing analysis with the new study[1] and excludes the study that had been included erroneously.[14]

- Sensitivity analysis 1 (Section 2.2). This analysis re-introduces (to the new primary analysis) studies that had been excluded based on the recruitment of patients from both primary and secondary care referrals, or for which it was unclear if they were recruited from both settings. This results in the study that had been erroneously included being reintroduced,[14] and one[12] of the two studies (to avoid potential double counting) from the company's reference list being included. Since the committee made research recommendations for FOB Gold, the EAG has provided this analysis for their consideration, but caution that the generalisability of these two studies to symptomatic patients referred from primary care is not clear and the primary analysis may still be preferred.

A further sensitivity analysis has been conducted:

- Sensitivity analysis 2 (Appendix A). This analysis removes one study (Benton et al 2022)[18] from the FOB primary analysis because of concerns about its generalisability and impact on results.

The analysis of all tests together, which informed the comparator arm in the modelling, has also been updated to reflect the changes to the FOB Gold new primary analysis and new sensitivity analysis.

3 New FOB Gold syntheses

3.1 New primary analysis for FOB gold

The new study[1] recruited patients in primary care (n=3349, with 30 CRC events, prevalence 0.90%), in an area with a system that prompted GPs not to use FIT if a patient did not meet DG30 low risk criteria, but did not prevent FIT requests outside DG30 low risk criteria. The study has therefore been classed as Type 4 as it includes some NG12 high risk patients, but may include predominantly DG30 low risk patients. Data at only one threshold were reported (10µg/g). It used a records follow-up reference standard.

The study that was removed[14] was a small study (n=163, with 26 CRC events, prevalence 15.95%) from Denmark which reported eight thresholds from 2-150 µg/g (see Table 1, Schwettmann 2022[14]). As noted previously, it recruited patients referred to colonoscopy from primary and secondary care and was a Type 4 study. The EAG had noted its high CRC prevalence (15.95%) in the original EAG report (Section 4.3.3), which may be due in part to recruitment of patients referred from secondary care.

The new primary analysis therefore includes three studies with 4135 patients and eight data points reported across four thresholds ranging from 2 to 150µg/g, with all reporting data at a threshold of 10µg/g. This increases the number of patients from 949 in the original analysis. However, there is a reduction in the data contributing to the pooled estimates at higher thresholds since the removed study (Schwettman *et al.* 2022[14]) provided data at eight thresholds from 10 to 150 µg/g, and the added study (Jordaan *et al.* 2023[1]) provided data at a threshold of 10µg/g only.

All three studies were from the UK. Two used FOB Gold Wide with the SENTiFIT 270 analyser, [10, 18] whilst one[1] stated the test to be FOB Gold and the analyser to be Roche Cobas c501 analyser (Roche Diagnostics, Oslo, Norway). It was not clear if the analysers would produce equivalent data. There was one Type 2 study[18] (NG12 high risk patients) and two Type 4 studies.[1, 10] The reference standard was imaging in two studies,[10, 18] and records follow-up in one.[1]

No diagnostic test accuracy data were reported for subgroups according to patient characteristics across all three studies, and there were no data on dual FIT using FOB-Gold.

Table 1: Study and patient characteristics of FOB-Gold studies

	Author, year Location Recruitment dates Study name (if available)	Analyser Reference standard	Inclusion criteria	Comparison to Scope	Mean/median age in years	Patient characteristics • Male; • Ethnicity; • Anaemia status	N with CRC/ N analysed (%)	Thresholds, µg/g	Subgroups
Primary analysis studies									
Population type 2 studies (NG12 High risk)									
1	Benton 2022[18] 50 NHS hospitals across England, UK Oct 2017 to Dec 2019 NICE FIT	FOB Gold Wide - SENTiFIT 270 Colonoscopy	NG12 high risk, who had colonoscopy. Randomised to cohort 1 who were given 4 tests	NR	NR	• NR • NR • NR	7/233 (3.00%)	2, 10, 100	None
Population type 4 (unclear/unrepresentative of all presenting to primary care)									
2	MacLean 2022a[10] Royal Surrey Foundation Trust, UK July 2019 and March 2020	FOB Gold Wide SENTiFIT 270 Colonoscopy or CTC or flexisig[a]	2WW referrals	NR	NR	• 48.8% • NR • NR	14/553 (2.53%)	10, 100, 150	None

3	Jordaan 2023[1] Mid-Yorkshire NHS Trust, Wakefield, UK Sept 2018 to the Dec 2019	FOB Gold, Roche Cobas c501 analyser Records follow-up	Mainly DG30 low risk, but some NG12 high risk	NR	NR	• 48% • NR • NR	30/3349 (0.90%)	10	None
Sensitivity analysis studies									
Population type 4 (unclear/unrepresentative of all presenting to primary care)									
4	Schwettmann 2022[14] Alesund Hospital, Norway January 2020 to February 2021	FOB Gold + Roche Cobas 8000 c702 analyser (Roche Diagnostics, Oslo, Norway) Colonoscopy	Referred to colonoscopy	NR	NR	• NR • NR • NR	26/163 (15.95%)	10, 15, 20, 30, 40, 50 ,100, 150	None
5	Navarro 2020[12] Spain, Zaragoza Nov 2016 to June 2018.	FOB Gold, analyser NR Colonoscopy	Referred to colonoscopy	NR	Mean 58.5 ± 14.9 years	• 44.3% • NR • 12%	36/727 (4.95%)	20	None

[a] **Maclean 2022a:** flexisig if presenting with perianal symptoms or anorectal bleeding

3.1.1 Quality assessment

The quality of the new study was subject to the same criticisms as other studies of similar design. That is to say, the records follow-up reference standard may have missed some false negative cases. It was also unclear if a consecutive sample was recruited. Overall, the evidence base was at some risk of bias as indicated by Table 2.

3.1.2 FOB gold new primary analysis synthesis

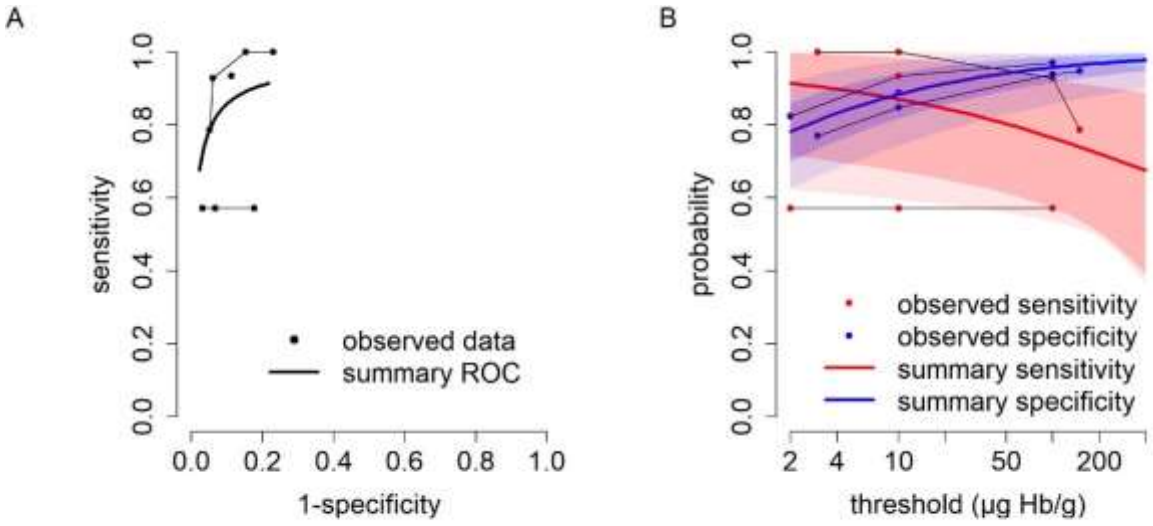
The original analysis has been updated to exclude Schwettmann *et al.* 2022 and include Jordaan *et al.* 2023.

Three studies contributed to the meta-analysis for FOB Gold (Benton *et al.* 2022, Maclean *et al.* 2022a, Jordaan *et al.* 2023). The number of thresholds considered by each study ranged from 1 to 4 and the final dataset provided a total of 8 pairs of sensitivity and specificity, at thresholds between 2 and 150.

Figure 1 A displays the results on the ROC plane. Observations from the same study are joined by a line. Figure 1 B displays the sensitivity and specificity as a function of threshold. Due to the small number of studies evaluating FOB Gold subgroup analyses by population type were not conducted. Sensitivity and specificity for specific thresholds is summarised in

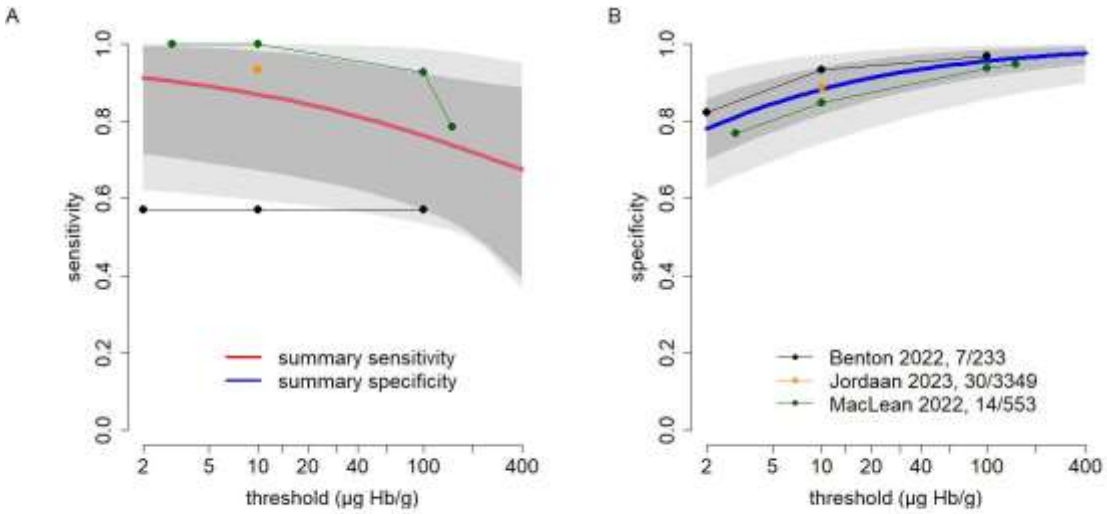
Table ***3***.

The summary sensitivity and specificity are also plotted in Figure 2, with information relating to the number of participants and number of positive tests in each study.



95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 1: Observed data and summary sensitivity and specificity for FOB Gold Primary analysis



95% credible intervals and predictive intervals for summary sensitivity and specificity are shown by the dark and light grey regions.

Figure 2: Observed data and summary sensitivity and specificity for FOB Gold Primary analysis, with study information

3.2 Sensitivity analysis 1

An additional two studies[12, 14] recruited patients referred to colonoscopy, but did not state if referrals were from primary and secondary care or primary care only. Both studies recruited only symptomatic patients and for this reason, and in accordance with the review inclusion criteria if no or little evidence

was identified, it was thought reasonable to include them in a sensitivity analysis, for consideration by the committee. Their characteristics are reported in Table 1.

The EAG notes that the CRC prevalence is relatively high/high in both studies (4.95%[12] and 15.95%[14]).

3.2.1 Quality assessment

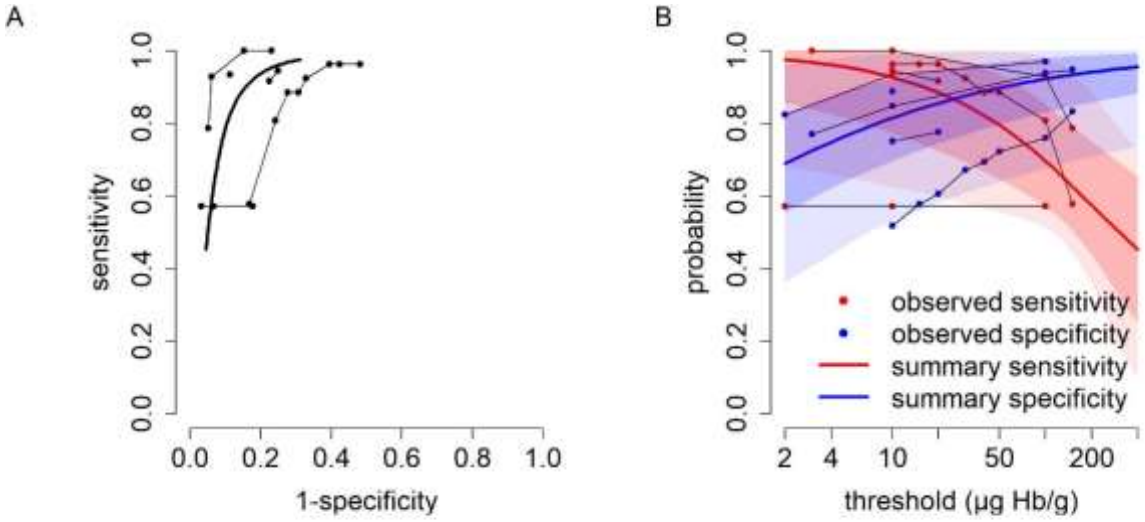
The two studies[12, 14] additionally included in the sensitivity analysis were at generally high or unclear risk of bias (Table 2).

3.2.2 FOB gold sensitivity analysis 1 synthesis

Five studies contributed to the sensitivity analysis. The number of thresholds considered by each study ranged from 1 to 8 and the final dataset provided a total of 18 pairs of sensitivity and specificity, at thresholds between 2 and 150.

Figure 3 A displays the results on the ROC plane. Observations from the same study are joined by a line. Figure 3 B displays the sensitivity and specificity as a function of threshold. Sensitivity and specificity for specific thresholds is summarised for all population groups in

Table ***3***.



95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 3: Observed data and summary sensitivity and specificity for FOB Gold Sensitivity Analysis

Table 2: FOB-Gold studies: ScHARR's assessment of risk of bias and applicability, with reasons for scores

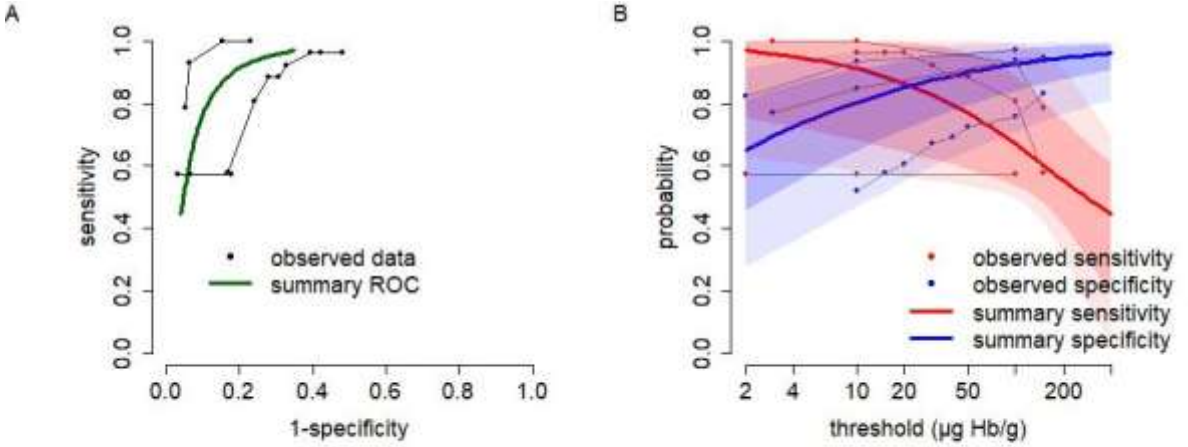
	Analyses [a]	RoB: Patient selection	RoB: Index test	RoB: Reference standard	RoB: Patient flow	Applicability risk: Patients and setting	Applicability risk: Index test	Applicability risk: Reference standard
Primary analysis studies								
Benton 2022[18]	2	High	Low	Unclear	Low	High	Low	Low
MacLean 2022a[10]	2	High	Low	Low	High	High	Low	Low
Jordaan 2023[1]	4	Unclear	Low	High	High	High	Low	Low
Sensitivity analysis studies								
Schwettmann[14]	4	Unclear	Low	Unclear	Unclear	High	Low	Low
Navarro 2020[12]	4	High	Low	Unclear	Unclear	High	Low	Low

[a] Numbers relate to population-type analyses.

3.3 Summary of updated synthesis results

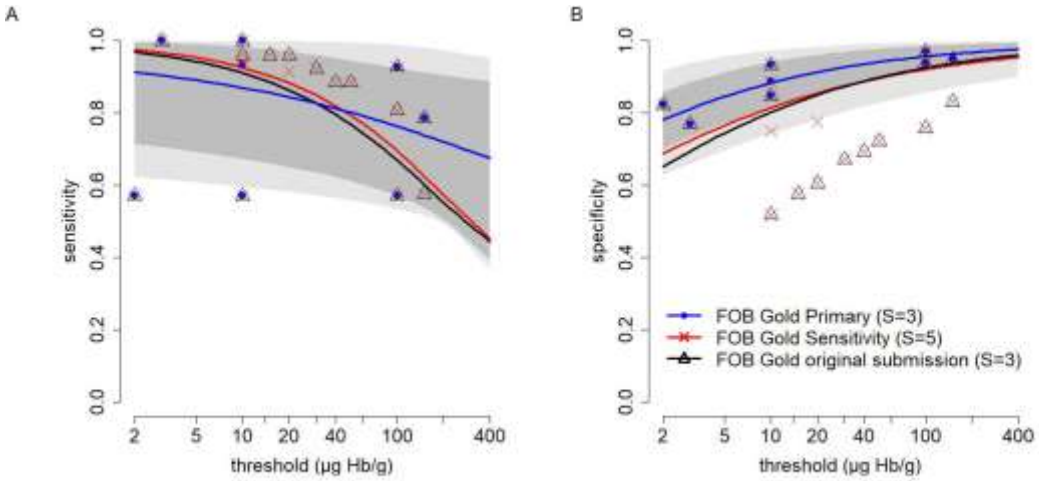
The results presented in the original submission are shown in Figure 4 for reference and all 3 analyses (the new primary, new sensitivity and original EAG analyses) are shown together in Figure 5.

In the updated primary analysis (blue line, Figure 5) the pooled sensitivity is slightly lower than the primary submission results (black line) at low thresholds, then higher from thresholds of 50 onwards. The removed study (Schwettmann *et al.* 2022)[14] had a very low sensitivity of 57.7% at threshold 150. By removing Schwettmann *et al.* 2022[14] from the new primary analysis, the pooled sensitivity at higher thresholds is greater than the previous analysis.



95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 4: Observed data and summary sensitivity and specificity for FOB Gold – analysis from original submission



95% credible intervals and predictive intervals for summary sensitivity and specificity of the primary analysis are shown by the dark and light grey regions.

Figure 5: Observed data and summary sensitivity (A) and specificity (B) for FOB Gold. Comparison of different analyses

Table 3: Summary sensitivity and specificity at selected thresholds for FOB Gold updated analyses

threshold	FOB Gold Primary (S=3, Benton 2022, Maclean 2022a, Jordaan 2023)		FOB Gold Sensitivity (S=5, Benton 2022, Maclean 2022a, Jordaan 2023, Schwettman 2022, Navarro 2020)		FOB Gold Original (S=3, Benton 2022, Maclean 2022a, Schwettmann 2022)		FOB Gold Primary without Benton (S=2, Maclean 2022a, Jordaan 2023)	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
2	91.4 (71.6,99.6)	78.1 (70,86)	97.6 (85.7,99.9)	68.9 (55.4,82.4)	96.9 (75.6,100)	65.2 (45.8,81.1)	98.7 (89.5,100)	76.6 (65,86.7)
2.5	90.9 (71.1,99.5)	79.9 (71.9,87.5)	97.2 (84.8,99.9)	70.9 (57.7,84.1)	96.4 (74.7,100)	67.6 (48.6,82.9)	98.5 (88.9,100)	78.3 (66.8,88.1)
3	90.5 (70.6,99.4)	81.2 (73.4,88.6)	96.8 (83.9,99.9)	72.4 (59.4,85.4)	96 (73.9,100)	69.5 (50.8,84.2)	98.3 (88.3,100)	79.7 (68.3,89.2)
4	89.8 (69.8,99.2)	83.2 (75.6,90.2)	96.1 (82.5,99.8)	74.8 (62.1,87.3)	95.1 (72.6,100)	72.4 (54.3,86.2)	97.9 (87.4,100)	81.7 (70.5,90.7)
7	88.2 (68.4,98.7)	86.5 (79.5,92.8)	94.2 (79.5,99.6)	79 (66.8,90.4)	93 (70,99.9)	77.5 (60.9,89.4)	96.9 (85.2,100)	85.2 (74.6,93.3)
10	87 (67.3,98.3)	88.4 (81.7,94.2)	92.7 (77.2,99.3)	81.5 (69.6,92.1)	91.2 (68.2,99.8)	80.3 (64.9,91.1)	96 (83.5,99.9)	87.1 (76.9,94.5)
20	84.5 (65.1,97.1)	91.3 (85.4,96.2)	88.4 (72.4,98.1)	85.6 (74.4,94.7)	86.4 (64.5,99.4)	85.1 (71.8,93.7)	93.7 (79.1,99.7)	90.2 (80.9,96.4)
50	80.3 (61.3,94.7)	94.2 (89.3,97.8)	79.4 (64.6,93.4)	89.8 (79.7,96.9)	76.9 (59.1,96.4)	89.9 (79.3,96.1)	88.3 (69.5,98.4)	93.3 (85.2,98)
100	76.4 (57.2,92.5)	95.7 (91.6,98.6)	69.6 (57,85.1)	92.2 (83,97.9)	67 (53.7,88.9)	92.6 (83.9,97.4)	82 (55.5,95.9)	95 (87.9,98.7)
120	75.3 (55.8,91.9)	96.1 (92.1,98.8)	66.5 (54.4,82.5)	92.7 (83.7,98.2)	64 (51.7,85.5)	93.2 (85,97.7)	79.9 (50.1,95)	95.3 (88.5,98.9)
150	73.9 (53.8,91.2)	96.4 (92.6,98.9)	62.5 (50.5,79.2)	93.3 (84.7,98.4)	60.2 (48.1,81)	93.8 (86.2,97.9)	77.1 (42.1,94)	95.8 (89.3,99)

*values in brackets are 95% credible intervals

3.4 Test uptake, failure and repeat test data from Jordaan 2023[1]

Test uptake was not reported. Only Jordaan *et al.* 2023[1] reported data on test failures and repeat tests. Of 3959 samples submitted to the laboratory, 610 (15.4%) could not be analysed. In 55%, this was due to buffer loss, 32.15% due to the wrong container having been used (it was thought to have been likely mixed up with the calprotectin tube), 4.7% had no label, 4.0% were overfilled and a further 4.2% for "diverse" reasons. Buffer loss was thought to be due to opening the tube at wrong end. This was thought by the Jordaan *et al.* 2023[1] authors not to be a problem with tubes used for a dedicated Sentifit analyser, but no data were supplied to support this view.

A repeat test was completed for 392/610 (64.2%) of the test failures.

4 All tests together analysis updated with changes to FOB Gold evidence base

The "all tests together" analysis informed the comparator arm in the model and has been updated to reflect the changes to the FOB Gold primary and sensitivity analyses.

4.1 Statistical synthesis of all tests – primary analysis

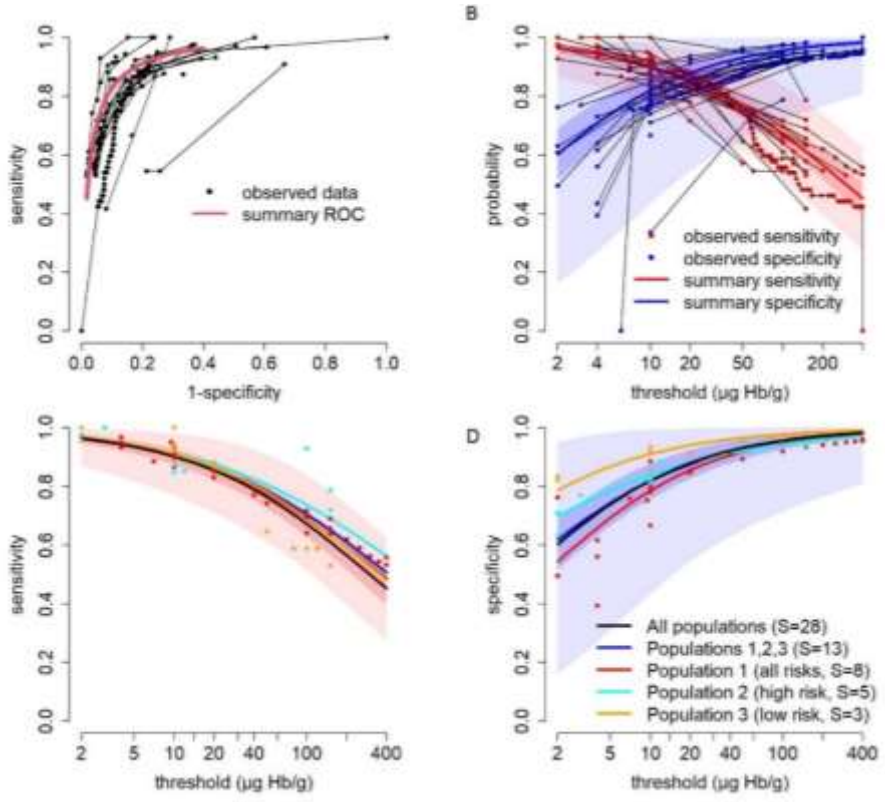
28 studies contributed to the new primary meta-analysis for all tests (OC-Sensor:11, HM JACKarc: 15, FOB Gold: 2, N.B. some studies were removed to avoid double counting of patients). 9 provided diagnostic accuracy at a single threshold and the maximum number of thresholds considered was 103. The final dataset provided a total of 194 pairs of sensitivity and specificity, at thresholds between 2 and 401.

Figure ***6*** A displays the results on the ROC plane.

Figure ***6*** B displays the sensitivity and specificity as a function of threshold. Pooled sensitivity and specificity are shown for subgroups based on population type in

Figure ***6*** C and

Figure ***6*** D respectively. Note that since the updated studies are type 4 only the pooled results for "all studies S=28" has changed since the previous analysis.



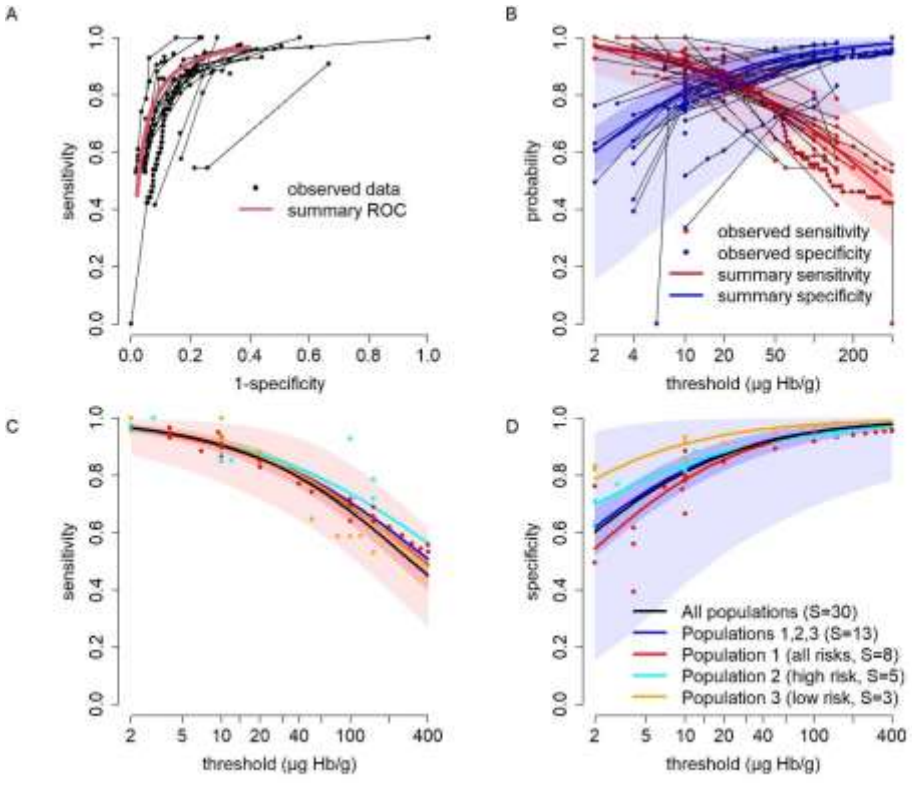
95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 6: Observed data and summary sensitivity and specificity for all tests together, primary analysis

4.2 Statistical synthesis of all tests – sensitivity analysis

30 studies contributed to the meta-analysis for all tests including studies that recruited referrals to colonoscopy from primary and secondary care for FOB Gold (Schwettman *et al.* 2022 and Navarro *et al.* 2020). (OC-Sensor:11, HM JACKarc: 15, FOB Gold: 4). 8 provided diagnostic accuracy at a single threshold and the maximum number of thresholds considered was 103. The final dataset provided a total of 201 pairs of sensitivity and specificity, at thresholds between 2 and 401.

Figure 7 A displays the results on the ROC plane. Figure 7 B displays the sensitivity and specificity as a function of threshold. Pooled sensitivity and specificity are shown for subgroups based on population type in Figure 7 C and Figure 7 D respectively Note that since the updated studies are Type 4 only the pooled results for "all studies S=30" has changed since the previous analysis.



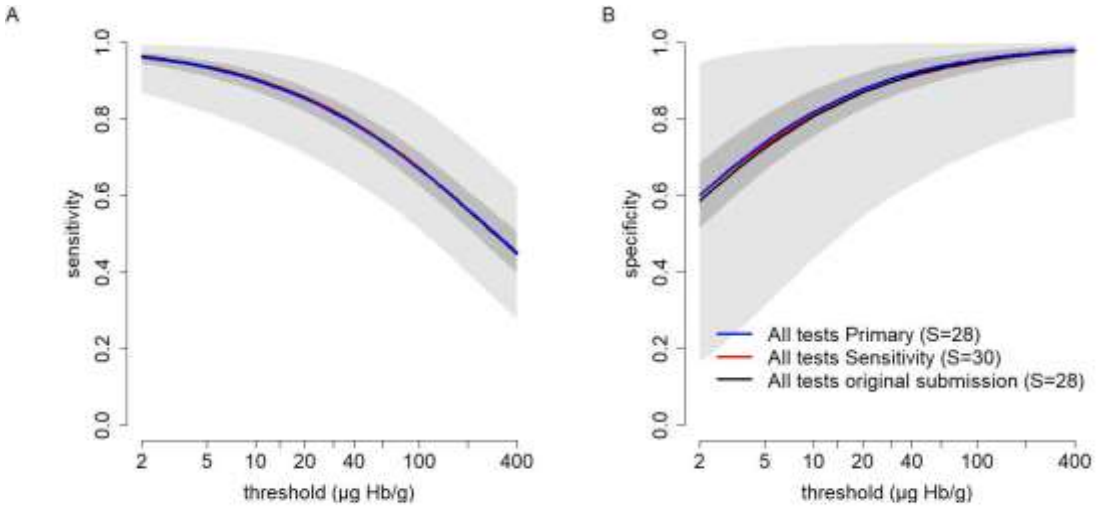
95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 7: Observed data and summary sensitivity and specificity for all tests together,

sensitivity analysis

4.3 Summary of updated results – all tests

The results of all 3 analyses are shown together in Figure 8. For all analyses the summary sensitivity and specificity are very similar at all thresholds.



95% credible intervals and predictive intervals for summary sensitivity and specificity of the primary analysis are shown by the dark and light grey regions.

Figure 8: Observed data and summary sensitivity (A) and specificity (B) for All tests. Comparison of different analyses

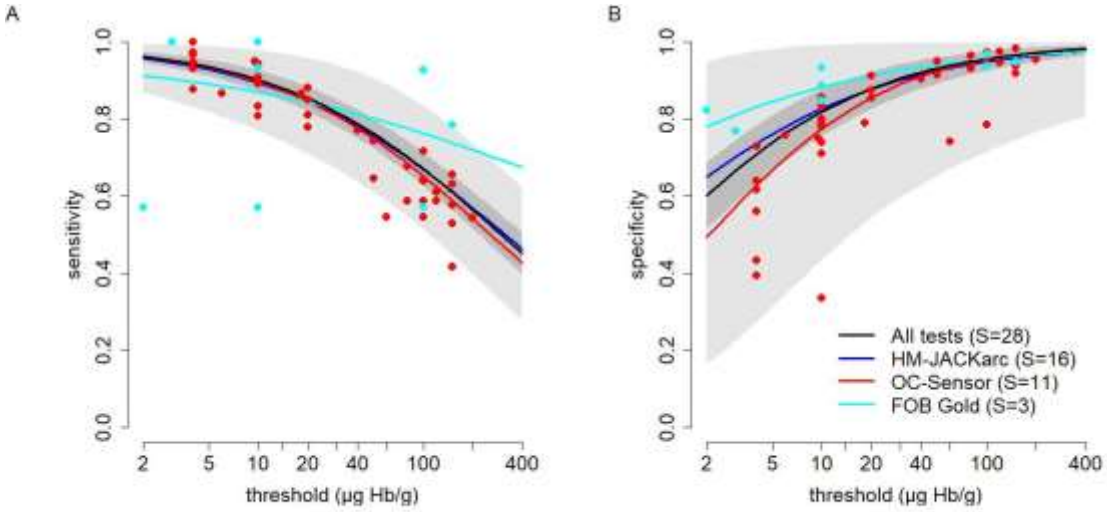
Table 4: Summary sensitivity and specificity at selected thresholds for all tests

threshold	All tests Primary (S=28)		All tests Sensitivity (S=30)		All tests Original (S=28)	
	Sensitivity *	specificity *	sensitivity *	specificity *	sensitivity *	specificity *
2	96.4 (94.7,97.7)	60.3 (51.6,68.8)	96.6 (95.1,97.9)	60.2 (51.9,68.7)	96.5 (94.8,97.8)	58.7 (49.9,67.4)
2.5	95.8 (94,97.2)	63.8 (55.5,72.1)	96.1 (94.4,97.5)	63.6 (55.5,71.8)	96 (94.1,97.4)	62.3 (53.7,70.7)
3	95.3 (93.4,96.9)	66.7 (58.6,74.7)	95.6 (93.8,97.1)	66.3 (58.4,74.3)	95.5 (93.5,97.1)	65.1 (56.8,73.3)
4	94.4 (92.3,96.2)	70.9 (63.2,78.4)	94.7 (92.7,96.4)	70.4 (62.8,77.9)	94.6 (92.4,96.4)	69.4 (61.4,77.1)
7	92.1 (89.6,94.3)	78.1 (71.3,84.6)	92.5 (90.1,94.6)	77.4 (70.5,83.9)	92.3 (89.7,94.6)	76.8 (69.7,83.5)
10	90.2 (87.4,92.7)	82 (75.7,87.8)	90.7 (88,93.1)	81.2 (74.8,87.1)	90.4 (87.6,93)	80.8 (74.3,86.8)
20	85.4 (82.2,88.5)	88 (82.7,92.5)	85.9 (82.8,88.9)	87.1 (81.7,91.8)	85.6 (82.3,88.8)	87.1 (81.6,91.8)
50	76.3 (72.5,80.1)	93.2 (89.3,96.2)	76.7 (73,80.4)	92.5 (88.3,95.6)	76.4 (72.5,80.3)	92.6 (88.5,95.8)
100	67.2 (62.8,71.5)	95.7 (92.7,97.7)	67.4 (63.4,71.5)	95.1 (91.8,97.4)	67.1 (62.8,71.4)	95.3 (92.1,97.5)
120	64.5 (60,68.9)	96.2 (93.4,98)	64.7 (60.5,68.9)	95.6 (92.5,97.7)	64.4 (60,68.7)	95.8 (92.8,97.8)
150	61.1 (56.4,65.7)	96.7 (94.1,98.4)	61.2 (56.8,65.6)	96.2 (93.3,98)	60.9 (56.3,65.4)	96.4 (93.6,98.2)

*values in brackets are 95% credible intervals

4.4 Summary of meta-analysis of diagnostic test accuracy

The summary sensitivity and specificity for each test type are illustrated in Figure 9. The results for HM-JACKarc and OC-Sensor have not changed since the original submission.



95% credible intervals and predictive intervals for summary sensitivity and specificity of analysis including all tests are shown by the dark and light grey regions.

Figure 9: Summary of all primary syntheses. FOB Gold and All tests updated

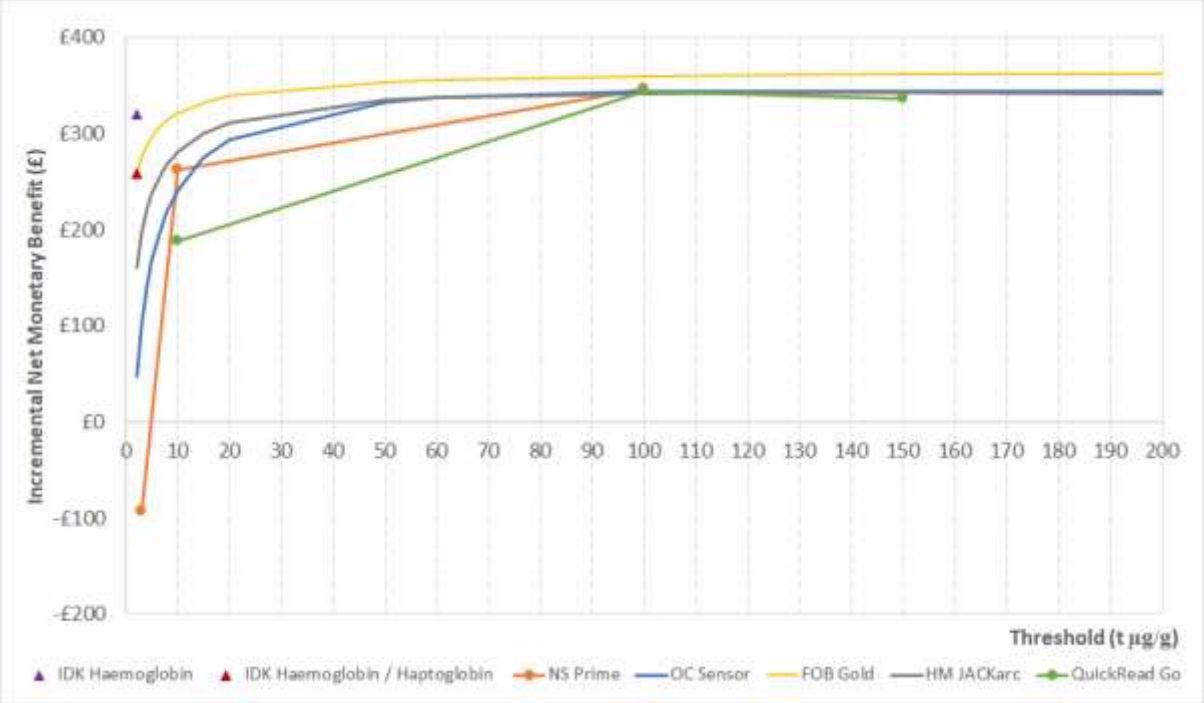
5 Updated results for the EAG cost-effectiveness results

The EAG updated the model results for the FOB Gold test following the changes in the synthesis reported in Section 2. These include the results generated from the model using high or low intensity safety netting and assuming a willingness-to-pay threshold of £20,000 or £30,000 per QALY gained. The results using low intensity safety netting are presented in Section 5.1, whilst results using high intensity safety netting are presented in Section 5.2.

The synthesis for the comparator (Intervention 3) have not been updated in these new analyses, since they have a minimal effect on the results (these have been tested by the EAG but are not reported here for brevity), and in order to keep comparability to the results for the other brand tests reported in the EAG addendum[19]. Results for the scenario analyses originally run by the EAG (Section 5.3.9 of the EAG report) are also not reported in this addendum.

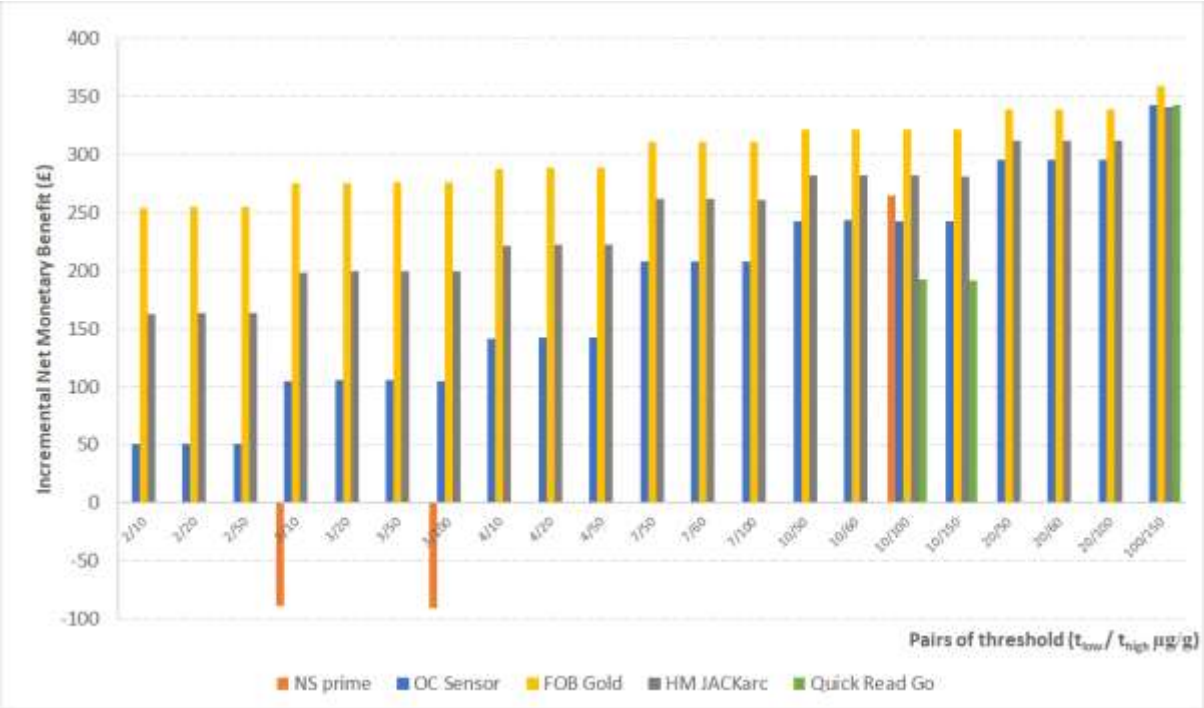
5.1 EAG's updated results for FOB Gold using low intensity safety netting

Figures presenting incremental net monetary benefit (iNMB) for the different tests are shown in Figure 10 to Figure 13 (Intervention 1 and Intervention 2 using willingness-to-pay thresholds of £20,000 or £30,000 per QALY gained). Tables with results for FOB Gold assuming a low intensity safety netting approach are presented in Table 5 (Intervention 1) and Table 6 (Intervention 2). Overall, the results are largely consistent with the original results presented in the EAG report and addendum, however, the iNMBs for FOB Gold increased for all thresholds used, when compared to the previous analyses.



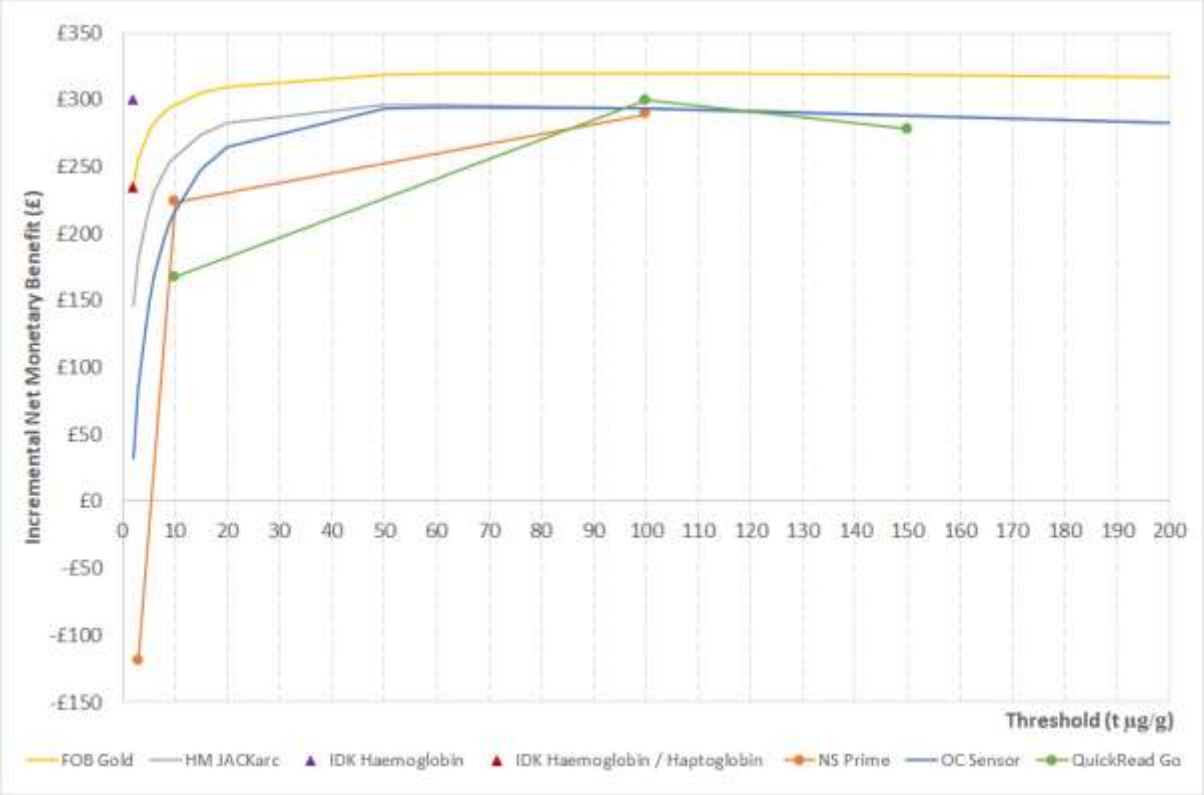
t – threshold

Figure 10: NMB for Intervention 1 assuming a threshold of £20,000 per QALY gained and low intensity safety netting (Figure 18 of the EAG report)



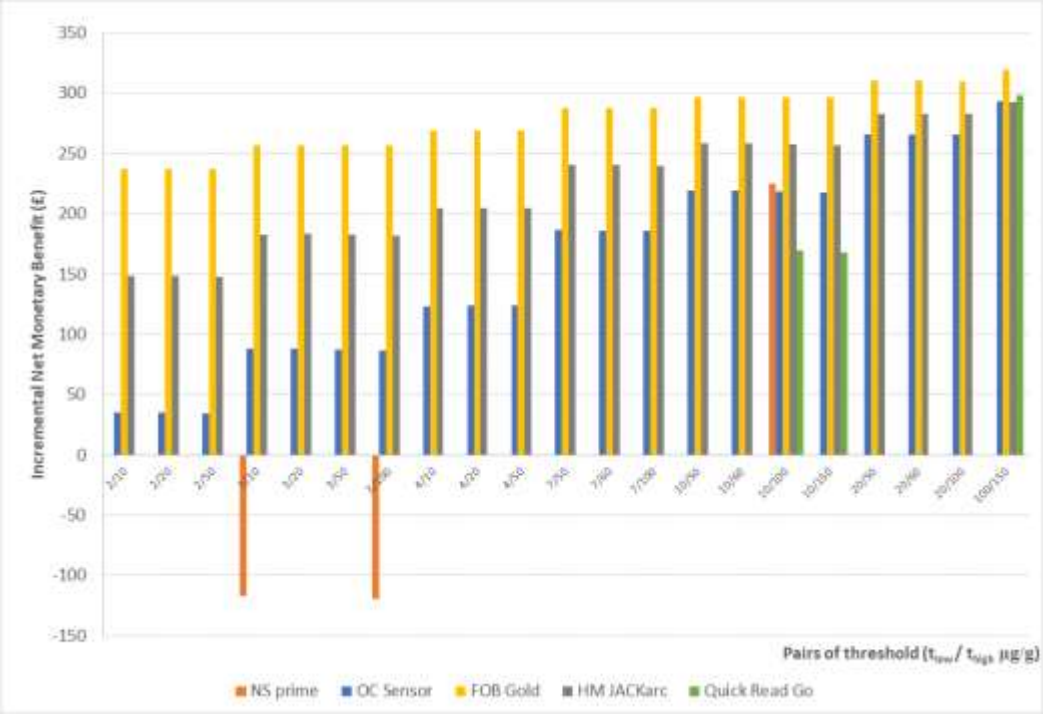
t_{low} – lower threshold; t_{high} – higher threshold

Figure 11: NMB for Intervention 2 assuming a threshold of £20,000 per QALY gained and low intensity safety netting (Figure 19 of the EAG report)



t – threshold

Figure 12: iNMB for Intervention 1 assuming a threshold of £30,000 per QALY gained and low intensity safety netting (Figure 26 of the EAG report)



t_{low} – lower threshold; t_{high} – higher threshold

Figure 13: iNMB for Intervention 2 assuming a threshold of £30,000 per QALY gained and low intensity safety netting (Figure 27 of the EAG report)

Table 5: Tabulated results for FOB Gold Intervention 1 (using one threshold, Table 52 of the EAG report): low intensity safety netting

	Int 1: FIT 1 threshold									Int 3 : DG30& NG12
t (µg/g)	2	4	5	7	10	20	50	60	100	10
LYs	14.166	14.166	14.166	14.165	14.165	14.165	14.164	14.164	14.164	14.168
QALYs	10.893	10.893	10.893	10.893	10.892	10.892	10.891	10.891	10.891	10.895
Costs (£)	£2,857	£2,817	£2,805	£2,789	£2,773	£2,747	£2,720	£2,715	£2,704	3143
ICER (pairwise, vs Intervention 3)† (£)	**171,656**	**168,018**	**164,954**	**159,118**	**151,575**	**138,691**	**121,615**	**118,454**	**110,019**	-
NMB λ=20,000 (vs Int 3) (£)	**252**	**287**	**297**	**309**	**321**	**339**	**353**	**355**	**359**	-
NMB λ=30,000 (vs Int 3) (£)	**236**	**268**	**276**	**287**	**296**	**310**	**319**	**319**	**319**	-
Number of 2WW referrals (total)	0.282	0.238	0.226	0.208	0.192	0.164	0.135	0.130	0.118	0.644
Number of 18WW referrals (total)	0.076	0.080	0.081	0.083	0.085	0.088	0.091	0.092	0.093	0.037
Number of Repeat FITs (total)	0.076	0.080	0.081	0.083	0.085	0.088	0.091	0.092	0.093	0.037
Number of Watch and Wait (total) (total)	0.567	0.601	0.611	0.625	0.638	0.660	0.683	0.687	0.696	0.281
Number of COLs (total)	0.328	0.293	0.283	0.268	0.255	0.232	0.208	0.204	0.194	0.623
Reduction in number of referrals (total - 2WW + 18WW)	47.6%	53.3%	54.9%	57.2%	59.4%	63.0%	66.8%	67.4%	69.0%	-
Reduction in number of referrals (2WW only)	56.3%	63.0%	64.9%	67.6%	70.2%	74.5%	79.0%	79.8%	81.6%	-
Increase in number of referrals (18WW only)††	101.7%	113.9%	117.4%	122.3%	127.0%	134.8%	142.9%	144.2%	147.6%	-
Reduction in number of COLs	47.4%	53.0%	54.7%	56.9%	59.1%	62.8%	66.6%	67.2%	68.9%	-
Mean time to diagnosis - CRC	2.659	2.787	2.835	2.916	3.013	3.234	3.612	3.697	3.963	1.384
Mean time to diagnosis - AAs	0.015	0.014	0.013	0.012	0.011	0.010	0.007	0.007	0.005	1.956
Mean time to diagnosis - IBD	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	2.044

†Southwest quadrant ICER; †† Also the value for increased repeat FITs and increased number of watch and waits

AA – advanced adenomas; COL - colonoscopy; CRC – colorectal cancer; FIT – quantitative faecal immunochemical test; IBD - inflammatory bowel disease; NMB – net monetary benefit; t – threshold;

Table 6: Tabulated results for FOB Gold Intervention 2 (using two thresholds, Table 53 of the EAG report): low intensity safety netting

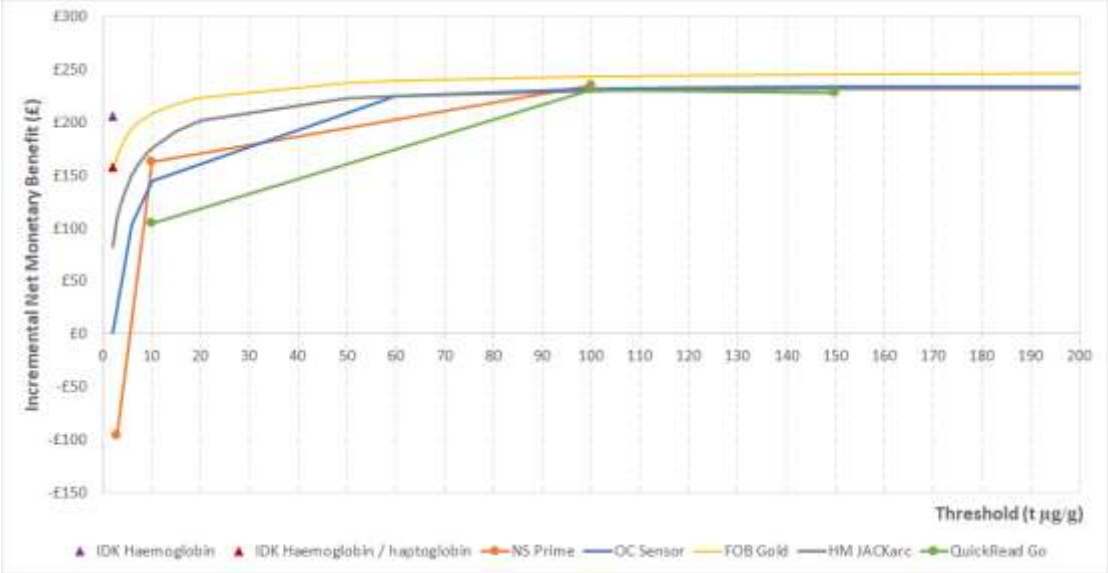
	Int 2: FIT 2 thresholds												Int 3: DG30 & NG12
t_{low}/t_{high} (µg/g)	**2/10**	**2/20**	**2/50**	**4/10**	**4/20**	**4/50**	**7/50**	**7/100**	**10/50**	**10/100**	**20/50**	**20/100**	**10**
LYs	14.166	14.166	14.166	14.166	14.166	14.166	14.165	14.165	14.165	14.165	14.165	14.165	14.168
QALYs	10.893	10.893	10.893	10.893	10.893	10.893	10.893	10.892	10.892	10.892	10.892	10.892	10.895
Costs (£)	£2,854	£2,853	£2,852	£2,815	£2,814	£2,813	£2,786	£2,786	£2,771	£2,771	£2,746	£2,745	3143
ICER (pairwise, vs Intervention 3)† (£)	**168,731**	**166,816**	**163,788**	**166,444**	**164,953**	**162,538**	**155,516**	**153,887**	**149,034**	**147,651**	**137,528**	**136,498**	-
NMB λ=20,000 (vs Int 3) (£)	**254**	**255**	**255**	**288**	**289**	**289**	**311**	**311**	**322**	**322**	**339**	**339**	-
NMB λ=30,000 (vs Int 3) (£)	**237**	**237**	**237**	**269**	**269**	**269**	**288**	**287**	**297**	**297**	**310**	**310**	-
Number of 2WW referrals (total)	0.267	0.263	0.259	0.231	0.227	0.222	0.197	0.194	0.183	0.180	0.159	0.157	0.644
Number of 18WW referrals (total)	0.085	0.088	0.091	0.085	0.088	0.091	0.091	0.093	0.091	0.093	0.091	0.093	0.037
Number of Repeat FITs (total)	0.080	0.082	0.083	0.083	0.084	0.086	0.087	0.088	0.088	0.089	0.090	0.090	0.037
Number of Watch and Wait (total) (total)	0.567	0.567	0.567	0.601	0.601	0.601	0.625	0.625	0.638	0.638	0.660	0.660	0.281
Number of COLs (total)	0.324	0.323	0.321	0.291	0.289	0.288	0.265	0.264	0.252	0.251	0.231	0.230	0.623
Reduction in number of referrals (total - 2WW + 18WW)	48.3%	48.5%	48.7%	53.6%	53.8%	54.1%	57.7%	57.9%	59.8%	60.0%	63.2%	63.4%	-
Reduction in number of referrals (2WW only)	58.5%	59.1%	59.9%	64.1%	64.8%	65.5%	69.4%	69.8%	71.6%	72.0%	75.2%	75.7%	-
Increase in number of referrals (18WW only)	127.0%	134.8%	142.9%	127.0%	134.8%	142.9%	142.9%	147.6%	142.9%	147.6%	142.9%	147.6%	-
Increase in number of repeat FITs	114.4%	118.3%	122.3%	120.4%	124.3%	128.4%	132.6%	135.0%	134.9%	137.3%	138.8%	141.2%	-
Increase in number of watch and waits	101.7%	101.7%	101.7%	113.9%	113.9%	113.9%	122.3%	122.3%	127.0%	127.0%	134.8%	134.8%	-
Reduction in number of COLs	48.0%	48.3%	48.5%	53.4%	53.6%	53.8%	57.5%	57.6%	59.6%	59.7%	63.0%	63.2%	-
Mean time to diagnosis - CRC	2.680	2.693	2.716	2.800	2.812	2.834	2.953	2.972	3.045	3.063	3.253	3.271	1.384
Mean time to diagnosis - AAs	4.495	4.546	4.612	5.140	5.188	5.250	5.912	5.953	6.409	6.449	7.240	7.278	1.956
Mean time to diagnosis - IBD	2.942	2.986	3.048	3.341	3.382	3.441	3.847	3.890	4.151	4.192	4.829	4.869	2.044

†Southwest quadrant ICER

AA – advanced adenomas; COL - colonoscopy; CRC – colorectal cancer; FIT – quantitative faecal immunochemical test; IBD - inflammatory bowel disease; NMB – net monetary benefit; t – threshold;

5.2 EAG's updated results for FOB Gold using high intensity safety netting

Figures presenting iNMBs for the different tests are shown in Figure 14 to Figure 17 (Intervention 1 and Intervention 2 using willingness-to-pay thresholds of £20,000 or £30,000 per QALY gained). Tables with results for FOB Gold assuming a high intensity safety netting approach are presented in Table 7 (Intervention 1) and Table 8 (Intervention 2). Similar to the results for the low intensity safety netting approach, the results are largely consistent with the original results presented in the EAG report and addendum, however, the iNMBs for FOB Gold increased for all thresholds used, when compared to the previous analyses.

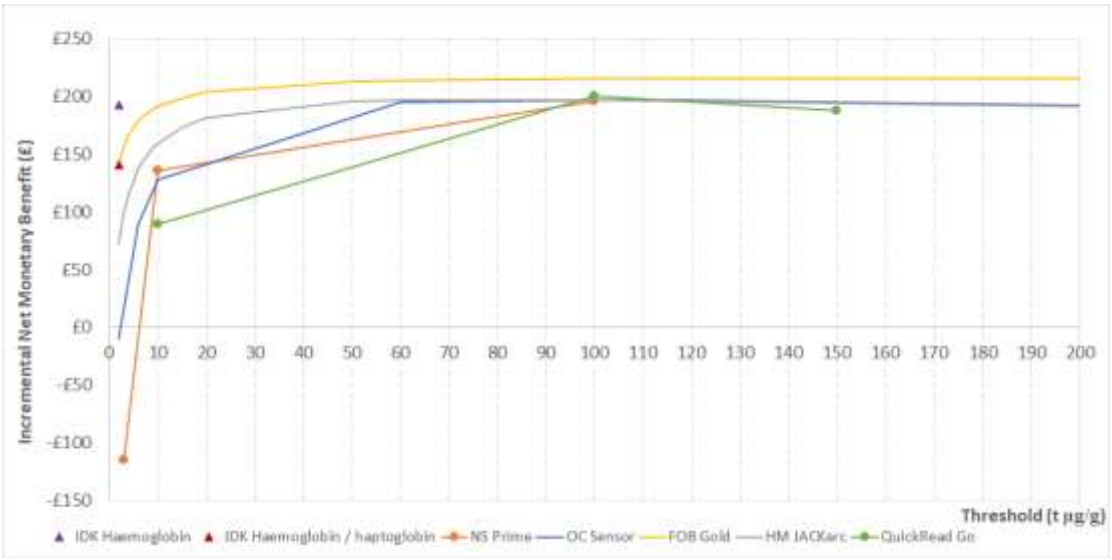


t – threshold

Figure 14: iNMB for Intervention 1 assuming a threshold of £20,000 per QALY gained and high intensity safety netting (Figure 24 of the EAG report)

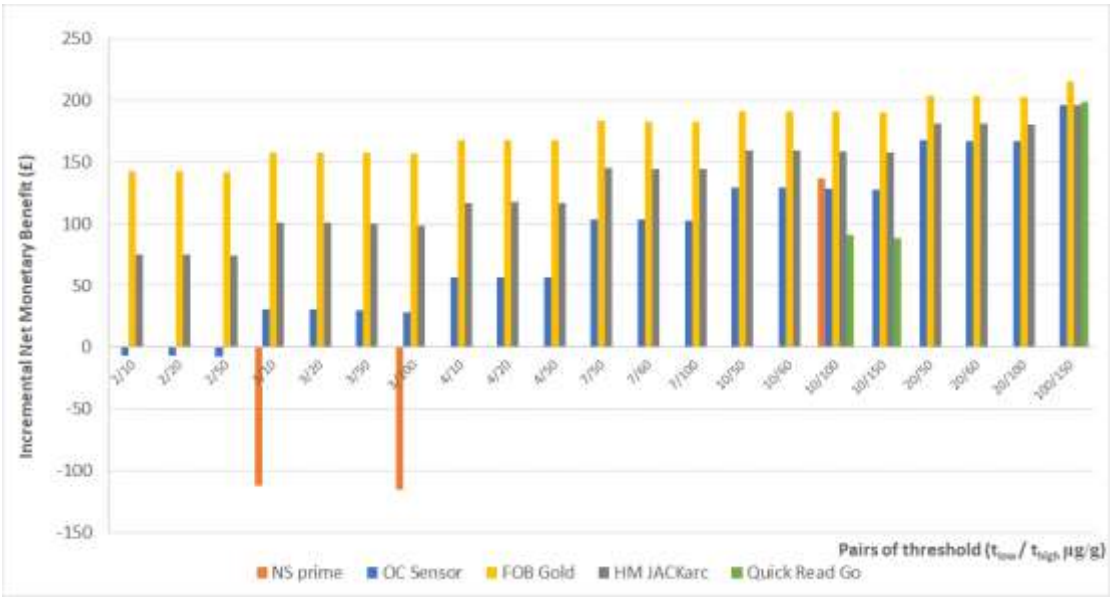
t_{low} – lower threshold; t_{high} – higher threshold

Figure 15: iNMB for Intervention 2 assuming a threshold of £20,000 per QALY gained and high intensity safety netting (Figure 25 of the EAG report)



t – threshold

Figure 16: iNMB for Intervention 1 assuming a threshold of £30,000 per QALY gained and high intensity safety netting (Figure 28 of the EAG report)



t_{low} – lower threshold; t_{high} – higher threshold

Figure 17: iNMB for Intervention 2 assuming a threshold of £30,000 per QALY gained and high intensity safety netting (Figure 29 of the EAG report)

Table 7: Tabulated results for FOB Gold Intervention 1 (using one threshold, Table 92 of the EAG report): high intensity safety netting

	Int 1: FIT 1 threshold									Int 3 : DG30 & NG12
t (µg/g)	**2**	**4**	**5**	**7**	**10**	**20**	**50**	**60**	**100**	**10**
LYs	14.167	14.166	14.166	14.166	14.166	14.166	14.165	14.165	14.165	14.168
QALYs	10.894	10.893	10.893	10.893	10.893	10.893	10.892	10.892	10.892	10.895
Costs (£)	3070	3038	3029	3016	3004	2983	2961	2957	2947	3,247
ICER (pairwise, vs Intervention 3)† (£)	148,531	150,910	149,609	146,215	140,970	131,395	117,299	114,581	107,182	-
NMB λ=20,000 (vs Int 3) (£)	153	181	189	199	209	224	237	239	243	-
NMB λ=30,000 (vs Int 3) (£)	141	167	174	183	191	204	213	214	216	-
Number of 2WW referrals (total)	0.357	0.319	0.307	0.292	0.277	0.252	0.226	0.222	0.211	0.681
Number of 18WW referrals (total)	0.189	0.200	0.204	0.208	0.213	0.220	0.228	0.229	0.232	0.094
Number of Repeat FITs (total)	0.151	0.160	0.163	0.167	0.170	0.176	0.182	0.183	0.186	0.075
Number of Watch and Wait (total) (total)	0.302	0.321	0.326	0.333	0.340	0.352	0.364	0.366	0.371	0.150
Number of COLs (total)	0.500	0.475	0.468	0.458	0.448	0.432	0.416	0.413	0.406	0.709
Reduction in number of referrals (total - 2WW + 18WW)	29.5%	33.0%	34.1%	35.5%	36.8%	39.1%	41.5%	41.9%	42.8%	-
Reduction in number of referrals (2WW only)	47.6%	53.3%	54.9%	57.2%	59.4%	63.0%	66.8%	67.4%	69.0%	-
Increase in number of referrals (18WW only)††	101.7%	113.9%	117.4%	122.3%	127.0%	134.8%	142.9%	144.2%	147.6%	-
Reduction in number of COLs	29.4%	32.9%	33.9%	35.4%	36.7%	39.0%	41.4%	41.8%	42.8%	-
Mean time to diagnosis - CRC	2.216	2.302	2.334	2.388	2.455	2.605	2.864	2.922	3.104	1.303
Mean time to diagnosis - AAs	3.683	4.159	4.343	4.645	5.007	5.608	6.380	6.529	6.909	1.956
Mean time to diagnosis - IBD	2.251	2.546	2.659	2.847	3.070	3.567	4.279	4.423	4.814	1.684

†Southwest quadrant ICER; †† Also the value for increased repeat FITs and increased number of watch and waits

AA – advanced adenomas; COL - colonoscopy; CRC – colorectal cancer; FIT – quantitative faecal immunochemical test; IBD - inflammatory bowel disease; NMB – net monetary benefit; t – threshold;

Table 8: Tabulated results for FOB Gold Intervention 2 (using two thresholds, Table 93 of the EAG report): high intensity safety netting

	Int 2: FIT 2 thresholds												Int 3[§]
t_{low}/t_{high} (µg/g)	**2/10**	**2/20**	**2/50**	**4/10**	**4/20**	**4/50**	**7/50**	**7/100**	**10/50**	**10/100**	**20/50**	**20/100**	**10**
LYs	14.167	14.167	14.166	14.166	14.166	14.166	14.166	14.166	14.166	14.166	14.166	14.166	14.168
QALYs	10.894	10.894	10.894	10.893	10.893	10.893	10.893	10.893	10.893	10.893	10.893	10.893	10.895
Costs (£)	3067	3066	3065	3037	3036	3035	3014	3013	3002	3001	2982	2981	3247
ICER (pairwise, vs Intervention 3)[†] (£)	144,411	141,790	137,732	148,441	146,181	142,620	140,399	137,888	136,714	134,493	129,328	127,557	-
NMB λ=20,000 (vs Int 3) (£)	155	155	156	182	182	182	200	200	209	209	224	224	-
NMB λ=30,000 (vs Int 3) (£)	143	143	142	168	168	167	183	183	191	191	204	203	-
Number of 2WW referrals (total)	0.343	0.339	0.334	0.311	0.307	0.302	0.280	0.278	0.268	0.265	0.247	0.245	0.681
Number of 18WW referrals (total)	0.199	0.201	0.204	0.205	0.208	0.211	0.216	0.218	0.219	0.220	0.223	0.225	0.094
Number of Repeat FITs (total)	0.156	0.157	0.159	0.163	0.164	0.166	0.170	0.171	0.173	0.174	0.178	0.178	0.075
Number of Watch and Wait (total) (total)	0.302	0.302	0.302	0.321	0.321	0.321	0.333	0.333	0.340	0.340	0.352	0.352	0.150
Number of COLs (total)	0.496	0.495	0.493	0.473	0.472	0.470	0.455	0.454	0.446	0.445	0.431	0.430	0.709
Reduction in number of referrals (total - 2WW+18WW)	30.1%	30.3%	30.5%	33.4%	33.6%	33.7%	36.0%	36.1%	37.2%	37.3%	39.3%	39.4%	-
Reduction in number of referrals (2WW only)	49.7%	50.3%	51.0%	54.3%	55.0%	55.6%	58.9%	59.3%	60.7%	61.1%	63.7%	64.1%	-
Increase in number of referrals (18WW only)	111.8%	115.0%	118.2%	119.1%	122.3%	125.5%	130.5%	132.4%	133.4%	135.3%	138.0%	139.9%	-
Increase in number of repeat FITs	108.1%	110.0%	112.0%	117.2%	119.1%	121.1%	127.4%	128.6%	131.0%	132.2%	136.8%	138.0%	-
Increase in number of watch and waits	101.7%	101.7%	101.7%	113.9%	113.9%	113.9%	122.3%	122.3%	127.0%	127.0%	134.8%	134.8%	-
Reduction in number of COLs	30.0%	30.2%	30.4%	33.2%	33.4%	33.6%	35.9%	36.0%	37.1%	37.2%	39.2%	39.3%	-
Mean time to diagnosis - CRC	2.240	2.256	2.282	2.317	2.332	2.358	2.435	2.458	2.494	2.517	2.629	2.652	1.303
Mean time to diagnosis - AAs	3.816	3.877	3.955	4.241	4.300	4.376	4.811	4.862	5.137	5.188	5.679	5.729	1.956
Mean time to diagnosis - IBD	2.334	2.385	2.458	2.598	2.647	2.718	2.986	3.039	3.187	3.238	3.634	3.684	1.684

[†]*Southwest quadrant ICER;* [§] DG30 & NG12

AA, advanced adenomas; COL, colonoscopy; CRC, colorectal cancer; FIT, quantitative faecal immunochemical test; IBD, inflammatory bowel disease; NMB, net monetary benefit; t, threshold

6 Conclusions

The changes to the FOB Gold primary analysis resulted in removing one small study and including a new moderate-large sized study. Compared to the original analysis, the new primary analysis includes more patients at a threshold of 10 µg/g, but fewer patients at higher thresholds. At a threshold of 10µg/g, the summary sensitivity is slightly lower compared to the original analysis (87% (95% credible interval (CrI) 67.3 to 98.3) compared to 91.2% (95% CrI 68.2 to 99.8)), but the summary specificity is higher (88.4% (95% CrI 81.7,94.2) compared to 80.3% (95% CrI 64.9,91.1)). At thresholds below 10µg/g sensitivity is also lower. At thresdholds at and above 50µg/g sensitivity becomes higher than in the original analysis, and specificity remains higher. The cost-effectiveness results, compared with the original "all tests" analysis comparator arm in the addendum to the EAG's report, [19] show slightly higher iNMBs across all thresholds at willingness to pay thresholds of £20,000 and £30,000 per QALY. This is the case for both Intervention 1 and Intervention 2 and when assuming high or low intensity safety netting.

The diagnostic test accuracy sensitivity analysis including studies that also recruited/possibly recruited patients referred from secondary care is provided for consideration, but the EAG cautions that the generalisability of these studies is not clear. The summary sensitivity and specificity of this analysis are similar/slightly higher than the original analysis. For brevity, cost-effectiveness results were not provided for this analysis but the EAG notes that an increase in both sensitivity and specificity will inevitably result in higher iNMBs compared to the original analysis.

The results of the analysis of "all tests", which informed the comparator arm in the cost-effectiveness model, were very similar in the updated analysis compared to the original submission. Therefore, updated cost effectiveness results for each individual test were not provided for brevity, but were run by the EAG, and were very similar to the values presented in the EAG's first addendum.[19]

In conclusion, the new FOB Gold data provided additional evidence on FOB Gold, and improved the iNMB at both willingness to pay thresholds and for both intervention 1 and 2. The EAG's overall conclusions relating to the cost-effectiveness model results for all tests and all thresholds do not change.

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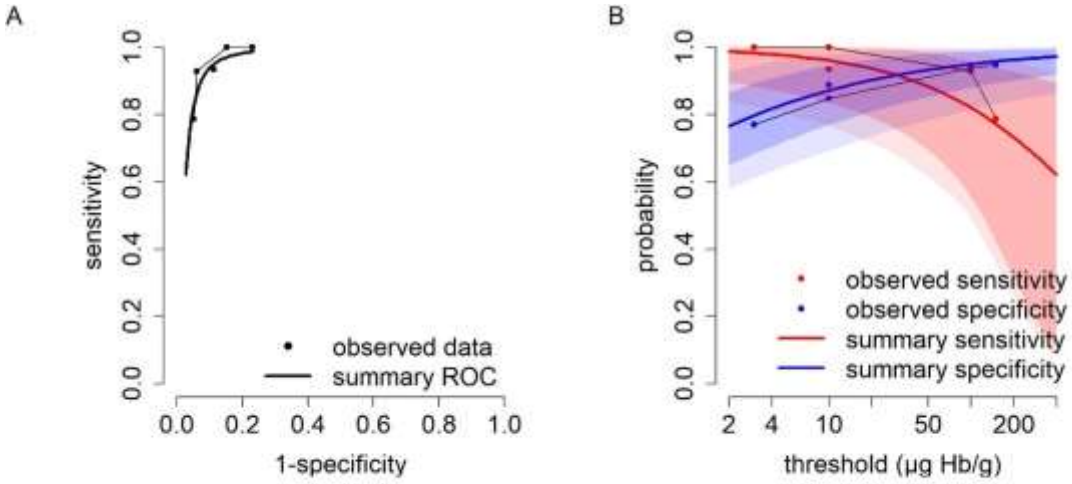
9 Appendix A: Sensitivity analysis 2 (removing Benton 2023)[18]

In this analysis one study[18] has been removed from the new primary analysis. In the original EAG report, the EAG felt this study should be included, but acknowledge that it does have the potential to confuse the visual interpretation of the plot, which did not provide a "weight" for each of the studies to contextualise their importance in the analysis. In addition, the patient spectrum may have been affected by the requirement to complete four tests, as detailed in the following paragraph.

Benton *et al.* 2022[18] was a NICE FIT study that included only NG12 high-risk patients from NICE FIT, and randomised patients who agreed to participate into one of two groups, each with a different objective. One group aimed to compare four different tests (OC-Sensor, HM-JACKarc, FOB Gold and NS Prime), and patients were asked to take four samples from the same stool. The patients in the analysis were those who were invited to and returned all 4 samples. The original NICE FIT study included 7194 high risk patients,[20] whilst the FOB Gold analysis included only 233 patients, and there were only 7 CRC events in this group. The requirement to complete four samples may have resulted in a different patient spectrum within the study, but has also resulted (possibly by chance) in faecal haemoglobin measurements for patients with colorectal cancer clustered around two extremes. Four cancer patients had results >100µg/g and three had values <20µg/g as measured by all analysers, and <2 as measured by HM-JACKarc and FOB Gold (personal communication with Sally Benton, 4th May 2023). The three values <2 µg/g result in a "flat line" in sensitivity estimates between 2 and 100 µg/g for both HM-JACKarc and FOB Gold.

Two studies therefore contributed to the meta-analysis (Maclean *et al.* 2022a, Jordaan *et al.* 2023).[1, 10] MacLean *et al.* 2022a considered 4 thresholds and Jordaan *et al.* 2023 considered 1 threshold. The final dataset provided a total of 5 pairs of sensitivity and specificity, at thresholds between 3 and 150. Summary sensitivity and specificity are shown in Figure 18. The numerical results are provided in Table 3.



95% credible intervals and predictive intervals for summary sensitivity are shown by the dark and light red regions. 95% credible and predictive intervals for summary specificity are shown by the dark and light blue regions

Figure 18: Observed data and summary sensitivity and specificity for FOB Gold excluding Benton (S=2)