2022 exceptional surveillance of impact of faecal immunochemical tests research on NICE guidance (NICE guideline NG12 and NICE diagnostics guidance DG30)

Surveillance proposal

The paused diagnostics assessment of quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036) will be resumed, and rescoped. The paused diagnostic assessment will aim to fully explore the application of FIT tests for triaging patients with suspected colorectal cancer with the purpose of identifying patients who are most at risk and optimising further investigation strategies such as colonoscopy.

We will also update section 1.3 colorectal cancer in the guideline on Suspected cancer: recognition and referral (NICE Guideline NG12) after the publication of the paused diagnostic assessment (GID-DG10036).

No new evidence was found to suggest that the recommendations on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care (diagnostics guidance DG30) should be changed. A post-publication update will remove recommendation 1.4 on the RIDASCREEN assay, as this test was discontinued in 2020 and is no longer available.

Reasons for the proposal

We decided that the paused diagnostics assessment of quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036) will be resumed, potentially followed by an update of the guideline (NICE Guideline NG12) to include the application of FIT tests in primary care if that is considered appropriate, as part of a triaging system for further investigations of suspected colorectal cancer.

In the current guideline, FIT tests are only offered to patients with a lower risk profile of colorectal cancer, based on the evidence evaluated in the Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care guideline (NICE Diagnostic Guidance DG30) to identify patients who may be at risk of colorectal cancer (recommendation 1.3.4). It is only one of several criteria which qualify people to be referred under the suspected cancer pathway for colorectal cancer (recommendation 1.3.1-1.3.4 and 1.13.2). Not all patients referred through the pathway would be offered a FIT.

Intelligence gathering through stakeholder feedback and the previous surveillance review in 2020 had alerted us that FIT could play an important additional role in triaging people referred through the colorectal cancer referral pathway for further investigations, particularly for colonoscopy. Changes have been made to the triaging of suspected colorectal cancer during the COVID-19 pandemic which may have an impact on the paused diagnostics assessment (GID-DG10036) and on NICE Diagnostics Guidance DG30.

New evidence on the accuracy, applicability, and interpretation of FIT results for estimating the risk of colorectal cancer is now available. The results of a large (n=9,822), double-blinded, multicentre study suggests that FIT is useful for triaging patients referred through the NICE guideline NG12's colorectal referral pathway. Different FIT thresholds could be used for different purposes. The study demonstrated the impact of using a low threshold (2 mcg/g) to rule out cancer, and a high threshold (150 mcg/g) to identify those who are most at risk of cancer. In addition to the study, a focused literature search found a substantial number of recently published studies relevant to this area.

Reason for the exceptional review

To explore the impact of the recently published NICE-FIT study that was identified during the surveillance review of the guideline in 2020. This study evaluated the diagnostic accuracy of the FIT tests to triage (rule out cancer)

symptomatic patients for a suspected cancer referral for bowel cancer in primary care.

Further focused literature searches on this topic area were conducted after topic experts' advice, to try to identify all relevant new evidence on the utility of FIT test in both primary and secondary care settings since the publication of NICE Diagnostics Guidance DG30.

For further details and a summary of all evidence identified in surveillance, see appendix A.

Methods

The exceptional surveillance process consisted of:

- Focused literature searches to identify relevant evidence.
- Considering the new evidence from the NICE-FIT study that triggered the exceptional review and other new evidence identified from the focused literature searches.
- Feedback from topic experts from the 2020 surveillance update, and queries raised in issues log.
- Requesting information from specialist committee members from the NICE Diagnostics Guidance DG30 assessment.
- Requesting information from manufacturers on changes to tests and clinical pathways since NICE Diagnostics Guidance DG30 publication.
- Considering relevant information from previous surveillance reviews of the NICE guideline NG12 guideline in 2020.
- Considering the evidence used to develop the NICE guideline NG12 in 2015.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research within the UK.

- Assessing the new evidence and/or information against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders.
- Considering comments received during consultation and making any necessary changes to the proposal.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

See Appendix A for details.

Search and selection strategy

We searched for new evidence related to the diagnostic accuracy and clinical effectiveness of FIT tests when used as a triage in a programme to guide referral for colorectal cancer. In addition, we also search for evidence related to the accuracy or validation of prediction models that included FIT and other risk factors (e.g. age, sex, symptoms and other risk factors), as we have been alerted by topic expert that these studies maybe available and are potentially important to current practice.

We found 2440 studies in a search for diagnostic accuracy studies, randomised controlled trials and prediction model studies published between 1 January 2016 and 20 February 2022. After applying additional criteria of study designs, 168 publications were initially included. After further assessments based on abstracts and applying criteria on relevance (location of study and whether patients were symptomatic), a total of 57 publications are included in this exceptional review.

See appendix A for details of all evidence considered, and references.

Information considered in this exceptional surveillance review

New published evidence: NICE-FIT Study

The NICE-FIT study protocol details were obtained through stakeholders' consultation during the 2020 surveillance review and have been tracked as a surveillance event. This study has now been published in October 2020.

NICE-FIT study methods

The NICE-FIT study was a multicentre, double-blinded diagnostic accuracy study conducted in 50 hospitals across England between October 2017 to December 2019. The objective was assessing whether FIT could be used to rule out colorectal cancer (CRC) in symptomatic patients meeting NICE's 2-week wait (2WW) criteria recommended in Suspected Cancer: Recognition and referral (NICE guideline NG12).

All people referred from primary care with symptoms meeting the referral criteria in NICE guideline NG12 for suspected CRC and those referred to the 2WW due to other criteria but triaged by secondary care clinicians to require colonoscopy were included. All stool samples were analysed using a single HM-JACKarc analytical system. The colonoscopists were blinded to the results of the FIT tests. Patients with incomplete colonoscopy, or with FIT returned only after the colonoscopy, were excluded from analyses.

The study is at relatively low risk of bias. The main concern is the relatively low proportion of eligible participants returning a stool sample for FIT testing (62.6%) and providing data that is eligible for analysis (46.5%); this may have some implications for the generalisability of the findings to actual clinical practice.

NICE-FIT results

A total of 21,126 participants were eligible for the trial; 9,822 completed both the FIT and colonoscopy and were included in the final analysis (46.5%). The final analysis reported the breakdown of diagnoses from the colonoscopy, and colorectal cancer was detected in 3.3% (n=329) of the participants, whereas 31.3% (n=3,079) were normal. Another 4.3% (n=421) had high risk adenoma,

while 2,321(23.6%) had low risk adenoma. The rest of the participants had other conditions such as diverticular disease (23.4%), perianal diseases (7.4%), inflammatory bowel disease (4.3%), microscopic colitis (1.5%), angiodysplasia (0.2%) and "others" (0.5%).

Three cut off thresholds for FIT were analysed at 2 mcg/g, 10 mcg/g and 150 mcg/g. At the lower cut off threshold of 2 mcg/g, sensitivity for detecting CRC was 97.0% (95% CI: 94.5% to 98.5%), correctly detecting 319 cases of CRC but with a high number of false positives (3,336 false positive cases), and the number needed to scope (NNS) was 11.5 scopes per cancer detected. When the threshold was increased to 10 mcg/mg (which is the threshold recommended in NICE's diagnostics guidance DG30 for referring people with suspected CRC who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral), the sensitivity for detecting CRC was 90.9% (95% CI: 87.2% to 93.8%); the number of false positives dropped to 1,563 cases, and NNS reduced to 6.2. If the threshold is increased to 150 mcg/g, about 1 in three people who tested positive with FIT would have CRC diagnosed at colonoscopy (NNS=3.2). However, with a sensitivity of only 70.8% (95% CI: 65.6% to 75.7%) this means 29.2% (96/329) of cancer cases would have been missed at that threshold.

Impact of NICE-FIT findings

The authors of the study concluded that at a lower cut-off threshold (2 mcg/mg), the sensitivity of FIT to detect CRC is close to that of colonoscopy and could be used to rule out cancer. Raising the cut off threshold would reduce the number of patients needed to attend the colonoscopy. Therefore, the use of FIT test could help to identify higher risk patients who should be prioritised for further investigations. If FIT testing were to be carried out in primary care, these findings would impact on current recommendations 1.3.1 to 1.3.3 in Suspected cancer: recognition and referral (NICE guideline NG12), where FIT test is currently not recommended to further triage patients who meet the 2WW referral criteria.

Moreover, this study also aligns with the objectives of the paused diagnostics assessment of quantitative faecal immunochemical tests to guide colorectal

cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036), and may provide evidence allowing the evaluation to continue.

Other published studies identified in focused literature search

See Appendix A for details.

The focused literature search identified a large volume of potentially relevant published studies (N=2,440). Therefore, additional criteria are used to exclude studies which might have a higher risk of bias or applicability concerns to focus on the most relevant and appropriately conducted studies. For example, we did not include studies with retrospective analysis of data for diagnostic accuracy studies, unless there is information to suggest the data from all patients were available and the follow-ups were. In addition, we only included cross sectional studies and excluded case-control studies. Studies evaluating the comparative effectiveness of triaging pathways would only be included if they were randomised trials. After further limiting studies to those that were conducted in the UK and other countries with similar epidemiology and healthcare settings (e.g. Europe, Australia, New Zealand, the United States of America and Canada) and are about patients with symptoms that could indicate CRC, 55 publications (with 2 studies included in two categories) are included in this exceptional review. These studies are summarised as follow:

- There were 34 publications (31 cross sectional, 3 cohort) of prospective diagnostic accuracy studies of FIT. Of these, 20 studies (analysing more than 40,000 participants) were conducted in the UK among symptomatic patients. The largest study was the NICE-FIT study (n=9,822). The other studies had sample sizes ranging from 238 to 5,250. Many of the UK studies applied FIT on participants who met the cancer referral criteria of the NICE guideline NG12, and reported the sensitivity and specificity at various thresholds and discussed the implications of using FIT as a triage for colonoscopy at these thresholds. These suggested that FIT triaging is useful for prioritising

colonoscopy, and there is flexibility to adjust thresholds depending on the stresses on the service.

- No RCT evidence of FIT versus alternative strategies among symptomatic participants was found.

- We found 10 publications reporting on the development and/or validation (accuracy) of five prediction models (a Dutch model, ColonFlag, FAST and COLONPREDICT COLONOFIT). These models incorporate additional clinical characteristics of patients into the interpretation of FIT in symptomatic participants to improve the accuracy of colorectal cancer detection.

In addition, we also found 11 systematic reviews on diagnostic accuracy of FIT including studies conducted in symptomatic participants and 2 systematic reviews on predictive models incorporating FIT for colorectal cancer.

Changes to diagnostic tests since NICE diagnostics guidance DG30 publication

- Minor software updates have been made for the OC Sensor PLEDIA analyser.

- OC Sensor uses a new control material which gives results at about 16 µg/g.

- Updated stability claims have been made for components of the FOB Gold test.

- The RIDASCREEN assay (assessed but not recommended in NICE diagnostics guidance DG30) is no longer available.

- Following development of NICE diagnostics guidance DG30, NICE became aware of the NS-Prime (Alfresa/Abbott) FIT. This test is included in the scope for GID-DG10036.

Information considered in previous surveillance of this guideline

The search from the previous surveillance in 2019/2020 was based on the original scope and only included evidence conducted in primary care settings. The NICE-FIT study was flagged as a potentially important ongoing study from topic experts.

The 2019/2020 surveillance review only identified one prospective observational study suggesting a combination of negative FIT (<10 mcg/g) result and a normal haemoglobin level was sufficient to rule out CRC. Given that it was only one observational study with a small number of patients included (n=373) it was considered that the evidence identified was insufficient to warrant an update of the recommendations in section 1.3 of NICE guideline NG12.

FIT was one of the most frequently mentioned topic by topic experts at the previous surveillance review (4 of 6 members who submitted detailed comments commented on FIT). Topic experts highlighted that the current recommendations on the use of FIT were not always adhered to in clinical practice. They commented that the use of FIT for symptomatic patients is an area of interest, and the evidence base was increasing quickly in the area of utility of FIT for helping to diagnose colorectal cancer. They suggested this topic should be put under frequent surveillance.

Information considered when developing the guideline

When the Suspected Cancer guideline was initially developed in 2015, the recommendation was to offer the faecal occult blood test (FOBT). The evidence was based on six diagnostic accuracy studies (n=9,871); five of these studies used guaiac based faecal occult blood tests (gFOBT) and only one study had used FIT (386 participants). Cost effectiveness modelling had shown that FOBTs were cost effective for people aged 40 years or older with a change in bowel habit.

NICE diagnostics guidance DG30 was published in 2017 and included evidence from 10 diagnostic cohort studies in people who had lower abdominal symptoms and were being investigated for possible colorectal cancer. Evidence was available for 3 different FITs (OC Sensor, HM-JACKarc and FOB Gold). A recommendation was made for adoption of these tests in primary care to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE guideline NG12, using a threshold of 10 mcg/g. Cost effectiveness modelling found that the FITs were cost effective compared with both guaiac-based FOBT and no triage.

The paused diagnostics guidance assessment GID-DG10036 was initiated to evaluate the use of FIT to triage people who do meet the criteria for the suspected cancer pathway but don't have rectal bleeding. It was paused during scoping due to changes in clinical pathways caused by the COVID-19 pandemic.

Other relevant NICE guidance

Published guidance:

Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care (DG30)

Colorectal cancer (NG151))

ColonFlag for identifying people at risk of colorectal cancer (MIB142)

Quality standards:

Suspected cancer (QS124), especially Quality statement 3: Testing for blood in faeces and potentially Quality statement 2: Urgent direct access endoscopy for oesophageal or stomach cancer

Guidance in Development:

Quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036)

Equalities

During the exceptional review process, it was noted that there may be cultural considerations regarding the acceptability of sampling a stool collection for FIT.

Stakeholder consultation

We are consulting with stakeholders on our proposal to re-launch the diagnostics assessment of quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036) and then update section 1.3 colorectal cancer in the guideline on Suspected cancer: recognition and referral (NICE Guideline NG12) .

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Overall proposal

We concluded that, based on the new evidence identified in this exceptional review, the role of FIT should be re-evaluated in NICE diagnostics guidance in development GID-DG10036 and NICE guideline NG12, with consideration given to the impact of different thresholds and additional risk factors in its interpretation. The current guidelines only recommend FIT for patients with lower risk profiles, and a positive test (at the 10 mcg/g threshold) is a qualifying criterion for the 2-week referral (2WW) colorectal cancer pathway for this group. A post-publication update to DG30 will remove recommendation 1.4 on the RIDASCREEN assay, as this test was discontinued in 2020 and is no longer available.

The event triggering the exceptional review (the NICE-FIT study) has suggested that FIT can also be used as a tool to triage patients who meet the 2WW referral criteria, and the possible use of varying thresholds to either rule out CRC, or to prioritise people with symptoms of CRC for colonoscopy. For example, different thresholds could be used simultaneously among patients who met the criteria for the 2WW colorectal cancer referral; with a low threshold value (e.g., 2 mcg/g) used to rule out CRC, and a high threshold (e.g., 150 mcg/g) used to identify patients who have the highest probability of having CRC and prioritise them for investigations.

In addition, the focused literature searches retrieved many studies which looked at the diagnostic accuracy and the application of FIT in triaging (with and without the consideration of other clinical risk factors). This included studies within the NHS to evaluate the implementation and impact of the current guidelines (NICE Diagnostics Guidance DG30, NICE guideline NG12) on various clinical and health service indicators, and the newer applications of FIT in triaging patients who met the existing 2WW colorectal cancer referral criteria.

An effective triaging tool could substantially reduce the number of people who are recommended for colonoscopy, which would help to reduce the waiting time to diagnosis for patients with suspected colorectal cancer, or other significant bowel conditions. Therefore, we propose that the diagnostics assessment of quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain (GID-DG10036) should be resumed, and the outcomes of this assessment then contextualised in the referral pathway in an update to NICE guideline NG12.