The faecal immunochemical test in low risk patients with suspected bowel cancer

ABSTRACT

The National Institute for Health and Care Excellence produced guidance recommending use of the faecal immunochemical test in patients with low risk symptoms for colorectal cancer. At a cut off of 10 μg haemoglobin per gram of faeces, the National Institute for Health and Care Excellence estimated that the sensitivity of the faecal immunochemical test to detect colorectal cancer ranged from 89% to 100%. The authors evaluated the evidence and noted that the data for the use of the faecal immunochemical test were extrapolated from all comers including high risk patients. Data on low risk patients were scarce and weak. Furthermore, faecal immunochemical test results vary by age, sex, deprivation, ethnicity and symptoms. Large national cohort studies are currently underway investigating the role of the faecal immunochemical test in the English population. Clear clinical pathways and rigorous safety netting are essential and should be part of implementing these guidelines to avoid missed cancers.

In July 2017 the National Institute for Health and Care Excellence released its diagnostic guidance DG30 on the use of the faecal immunochemical test in patients with symptoms who are at 'low risk' for colorectal cancer (National Institute for Health and Care Excellence, 2017). This article evaluates the evidence cited in DG30 that updated the previous NG12 guidance from 2015 (National Institute for Health and Care Excellence, 2015), and also assesses the impact of implementation which could overwhelm endoscopy services and could lead to missed cancers unless rigorous and closely monitored safety netting is put in place.

Colorectal cancer and the 2-week-wait pathway

Colorectal cancer is the third most common cancer in the UK. In 2015, 41 804 new cases of colorectal (also known as large bowel) cancer were diagnosed (Cancer Research UK, 2018). The NHS constitution gives patients the right to be seen by a specialist within 2 weeks of GP referral if cancer is suspected and symptoms meet specific criteria. In 2014–15, 262 745 patients were referred on the 2-week wait pathway with suspected colorectal cancer, of whom 93.5% were seen within 14 days (NHS England, 2016).

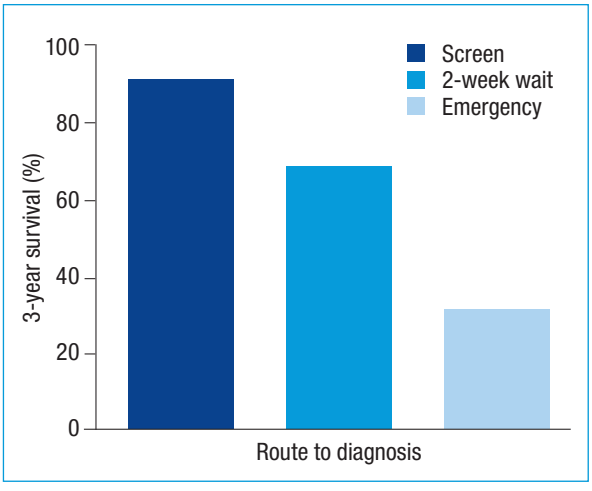
The 2-week wait pathway was established to enable detection and subsequent treatment of cancers at an earlier stage, which is essential to improve a patient's chance of cure. Twenty five per cent of patients with bowel cancer are diagnosed during an emergency presentation (National Cancer Intelligence Network, 2015), and these are usually at a more advanced stage. Their survival at 3 years is half that of patients referred by the 2-week wait (34% *vs* 68%), which is still not as good as that of patients diagnosed during bowel cancer screening (92%, *Figure 1*).

Who are the low risk patients?

Only 27–32% of patients with bowel cancer in England were identified via the 2-week wait referral route between 2008 and 2015 (National Cancer Intelligence Network, 2015), *vs* 25% who presented as an emergency. Organizations such as Bowel Cancer UK therefore called for guidelines to be expanded to include more patients who would then be eligible for fast-track referral (Bowel Cancer UK, 2014).

In 2015, the updated NG12 guidelines (National Institute for Health and Care Excellence, 2015) included two additional groups of symptoms: medium and low risk symptoms (*Table 1*). The low risk group (*Table 1*) comprised patients over 50 years of age with abdominal pain or weight loss, patients under 60 years of age with change in bowel habit or iron deficiency anaemia, or patients over 60 years of age with non-iron deficiency anaemia. The positive predictive value (or pre-test probability) for colorectal cancer in the group with 'medium risk' symptoms is 3–5% and less than 3% in the group with low risk symptoms, based mainly on retrospective evidence

Figure 1. Three-year survival for colorectal cancer according to route to diagnosis. From National Cancer Intelligence Network (2015).



Mr Nigel D'Souza, Colorectal Research Fellow, Department of Colorectal Surgery, Croydon University Hospital, Croydon CR7 7YE

Mr Muti Abulafi, Consultant Colorectal Surgeon, Department of Colorectal Surgery, Croydon University Hospital, Croydon

Correspondence to: Mr N D'Souza (nigel.d'souza@nhs.net)

Table 1. Referral symptoms as per National Institute for Health and Care Excellence guidance

Symptoms	2005 guidance (CG27)	2015 guidance (NG12)	2017 guidance (NG12 revised post-DG30)	Risk of cancer
■ Rectal bleeding for 6 weeks (>60 years old) ■ Rectal bleeding + diarrhoea for 6 weeks (>40 years old) ■ Change in bowel habit for 6 weeks (>60 years old) ■ Mass (any age) ■ Iron deficiency anaemia	Refer	Refer	Refer	High: >5%
■ Abdominal pain AND weight loss (>40 years old) ■ Rectal bleeding (>50 years old) ■ Rectal bleeding + (iron deficiency anaemia or change in bowel habit or weight loss, <50 years old) ■ Iron deficiency anaemia (>60 years old) ■ Change in bowel habit (>60 years old)		Refer	Refer	Medium: 3–5%
■ Abdominal pain OR weight loss (>50 years old) ■ Change in bowel habit (<60 years old) ■ Iron deficiency anaemia (<60 years old) ■ Anaemia, non-iron deficiency anaemia (>60 years old)		Test for occult blood (guiac-based faecal occult blood test)	Test for occult blood (faecal immunochemical test)	Low: 1–3%
Other symptoms			Test for occult blood (faecal immunochemical test, if no rectal bleeding)	?

evaluated by the National Institute for Health and Care Excellence Guideline Development Group (2015). The rationale for introducing these two lower risk groups of symptoms was part of a strategy by the National Institute for Health and Care Excellence to increase detection of colorectal cancer in symptomatic patients and decrease the number of emergency presentations with advanced stage disease. This strategy was also supported by Bowel Cancer UK (2014) in order to improve timeliness of diagnosis.

By including the cohort of patients with low risk symptoms, National Institute for Health and Care Excellence enabled this group to join the 2-week wait pathway. Previously these patients would have either been referred to secondary care on a routine pathway or managed in primary care depending on the GPs' clinical judgement. However, since the majority of 2-week wait patients are investigated by colonoscopy, National Institute for Health and Care Excellence (2015) recommended that patients with low risk symptoms should be tested first with a guaiac-based faecal occult blood test before referral to secondary care to avoid overwhelming endoscopy services. The faecal immunochemical test was not recommended in the original NG12 guidance in 2015 because of a paucity of evidence at the time. As the sensitivity of guaiac-based faecal occult blood test for colorectal cancer quoted by NG12 is 50% (National Institute for Health and Care Excellence, 2015), a referral to secondary care for further investigation for patients with low risk symptoms was therefore dependent on a test with the diagnostic accuracy of a coin toss. This was a controversial decision, challenged by experts (Steele et al, 2015), and was not adopted by regions such as London to avoid missing cancers in patients with false negative guaiac-based faecal occult blood test results. However, in 2017 the NG12 guidelines were revised to exclude low risk symptoms from the referral criteria, which were then incorporated into the newly developed DG30 guidance (National Institute for Health and Care Excellence, 2017). This recommended using the faecal immunochemical test to guide referral of patients with low risk symptoms.

What is the faecal immunochemical test?

The faecal immunochemical test is a dipstick test that detects the early degradation products of blood in the faeces, as a surrogate marker for colorectal cancer. The globin component of haemoglobin in stool is detected by immunoassay with labelled antibodies, forming a complex that can be measured. The qualitative faecal immunochemical test produces dichotomous positive or negative results. The National Institute for Health and Care Excellence (2017) evaluated the quantitative faecal immunochemical test formats, which measure faecal haemoglobin to the nearest microgram of haemoglobin per gram of faeces (μg/g). With the quantitative test, the cut offs for a 'positive' result and referral for investigation can be adjusted for higher sensitivity or specificity for colorectal cancer. Setting the cut off lower (e.g. at 10 μg/g) will result in more false positives (i.e. referral of patients with no significant disease on investigation), but fewer false negatives (missed cases of colorectal cancer). Setting the cut off higher (e.g. at 50 μg/g) will decrease the number of false positive referrals (and save further costs) but lead to more cases of missed colorectal cancer.

The faecal immunochemical test has a significantly higher sensitivity for colorectal cancer than guaiac-based faecal occult blood test in National Institute for Health and Care

Excellence (2015, 2017) modelling at 92–100% *vs* 50% respectively. The faecal immunochemical test carries other advantages over guaiac-based faecal occult blood test: easier and more hygienic specimen collection, one-off sampling and no false positive or negative results from dietary interference. The faecal immunochemical test is currently used or being rolled out in national bowel cancer screening programmes in over 43 countries around the world, and is due to be rolled out in England imminently (Schreuders et al, 2015).

What is the evidence for use of the faecal immunochemical test in patients with low risk symptoms?

The National Institute of Health Research Health Technology Assessment programme commissioned a diagnostic assessment report on the faecal immunochemical test to triage symptomatic patients at low risk of colorectal cancer presenting in primary care. The report was produced by an independent research company and published in June 2017 (Westwood et al, 2017).

This painstaking and thorough appraisal performed a clinical effectiveness review of the faecal immunochemical test, which looked at 10 studies published in 17 different publications. However, the review summarized the evidence from five studies only that reported on the faecal immunochemical test as a rule-out test for colorectal cancer with a cut-off threshold of 10 μg/g. Data were taken from one study (484 patients) for the HM-JACKarc analytical system, and four studies (4091 patients) for the OC-Sensor analyser. The summary estimate of sensitivity for the HM-JACKarc was 100% (95% confidence interval 71.5–100%) and for the OC-Sensor was 92.1% (95% confidence interval 86.9–95.3%). The corresponding specificity was 76.6% and 85.8%.

The review acknowledged that there were many limitations to the data included in the studies. The most notable limitation reported by the authors and highlighted in other reviews (Fraser, 2018) was the applicability of the population in the studies. None of the studies reported data for the population specified in the scope of the review with low risk symptoms. Instead, data were taken from studies that involved 'all comers' including high risk symptoms and routine referrals. As this population will have a different prevalence of bowel cancer, the sensitivity and specificity of the faecal immunochemical test in higher risk patients cannot reliably be extrapolated to low risk patients. The authors also noted that the studies included in the review were at unclear or high risk of bias in at least one domain on quality assessment. Furthermore, the only data on the faecal immunochemical test from England were published as a conference abstract. The review acknowledged that there was variation in optimal thresholds for the faecal immunochemical test in different countries and therefore data from studies outside of England may not be applicable to the English population (Fraser et al, 2014).

The review also studied the cost-effectiveness of the faecal immunochemical test. The model for HM-JACKarc was based on one study of 484 patients (Godber et al, 2016). As no cases of colorectal cancer (11/11) were missed in this study using a cut-off of 10 μg/g, the model assumed that it had a 100% sensitivity. The conference abstract from England in the review has since been published, which reports that colorectal cancer can be missed with HM-JACKarc (Widlak et al, 2017) with thresholds of 7 μg/g.

The review recommended that further large-scale studies were needed to fully evaluate the diagnostic accuracy of the faecal immunochemical test and despite the lack of evidence, suggested that the test could be used in low risk patients with a cut-off of 10 μg/g.

What are the National Institute for Health and Care Excellence (2017) recommendations?

The National Institute for Health and Care Excellence (2017) DG30 update based its guidance on the Health Technology Assessment review and recommended the use of the faecal immunochemical test in 'patients without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer'. This guidance does not make it clear exactly which patients should be tested with the faecal immunochemical test. The guidance probably refers to low risk patients as defined by NG12 guidelines upon its release in 2015. In 2017, upon release of the DG30 National Institute for Health and Care Excellence (2017) update, the NG12 guidelines were revised and the criteria for low risk patients were removed. Consequently, unless there is clear definition of the referral symptoms, it is likely to be interpreted by GPs as the statement suggests: any patient that does not meet the 2-week wait referral criteria, with any bowel or abdominal symptom (in the absence of rectal bleeding), irrespective of age, would qualify for testing with the faecal immunochemical test.

Traditionally, the National Institute for Health and Care Excellence produces guidance 'after careful consideration of the evidence available'. On this occasion, the absence of evidence for low risk patients led the DG30 committee to conclude that this led to 'uncertainty in the analysis', but that the introduction of the faecal immunochemical test should not wait until further research in these patients was conducted. A similar conclusion was reached on the possibility of subgroup variation in faecal haemoglobin values by age and sex.

The published discussion on potential false negatives (i.e. missed cancers) did not comment on certain assumptions of the model. It did not comment on the assumption that one analyser had 100% sensitivity. Nor did it discuss the model's assumptions on false negatives and delayed diagnosis, which were based on the opinions of three experts (out of 10 invited). This is particularly interesting given that the likely delayed diagnosis from falsely negative tests was one of the primary objections from a panel of leading, cross-specialty clinical experts and patient representatives to the role of guaiac-based faecal occult blood test in the 2015 guidance (Steele et al, 2015).

The committee did not mention any of the other limitations of the data, including those mentioned by the authors of the Health Technology Assessment report, such as the low number of patients in the included studies, the risk of bias in the included papers, or the extrapolation of data from studies outside of England.

Where could this lead us: problems and solutions

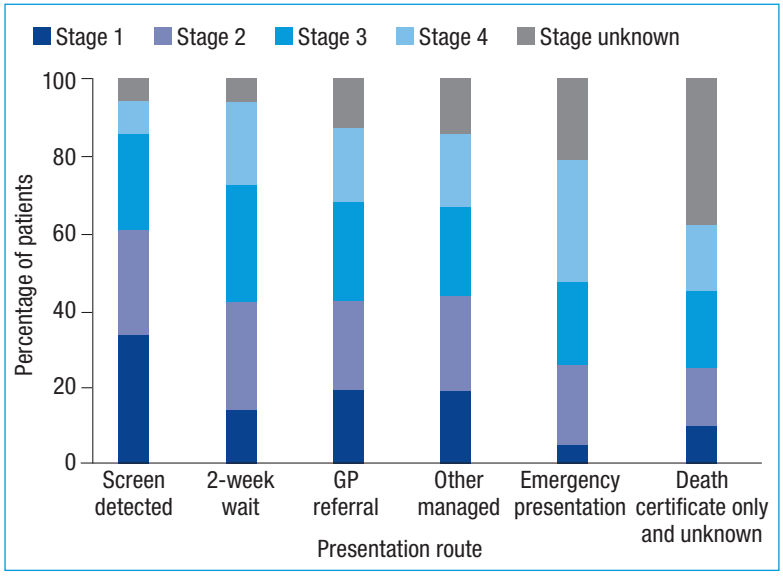
The evidence for the use of the faecal immunochemical test in patients with low risk colorectal symptoms is weak. The National Institute for Health and Care Excellence (2017) DG30 recommendations appear to be based on a pragmatic rather than a scientific assessment, in that doing something is better than doing nothing. If we are to assume that the DG30 recommendations from 2017 are targeting the low risk group from NG12 guidelines in 2015, it may be argued that this is a step in the right direction since the National Institute for Health and Care Excellence is recommending a better test (faecal immunochemical test *vs* guaiac-based faecal occult blood test) for these patients. However, literal interpretation of the guidance will introduce a much larger cohort of patients with nebulous, low risk bowel symptoms for faecal immunochemical testing. Many of these patients have until now been triaged for referral using their GP's clinical judgement, which resulted in cancer stage at diagnosis similar to patients diagnosed via 2-week wait pathways (*Figure 2*) (National Cancer Registration and Analysis Service, 2017b). Furthermore, testing this potentially enormous cohort of patients with the faecal immunochemical test is likely to increase the demand on endoscopy services because of the false positive results. Further strain on endoscopy capacity will jeopardise the capacity for colorectal cancer screening, which has the best survival of all routes to colorectal cancer diagnosis (National Cancer Registration and Analysis Service, 2017a).

Importantly, the issue of false negatives (i.e. missed cancers) has not been addressed adequately. Evidence now suggests that patient clinical characteristics may predict false negative results. In Scotland, 1378 symptomatic patients returned faecal immunochemical tests and underwent colonoscopy. There were seven patients with missed cancers: all these patients had iron deficiency anaemia (Digby et al, 2017). The same findings have emerged from a faecal immunochemical test pilot in Nottingham (Chapman et al, 2017). Furthermore, the variation in faecal haemoglobin levels as a result of age, sex (Fraser et al, 2014), deprivation (Digby et al, 2014) and aspirin usage (Allison and Fraser, 2011) as well as ethnicity, particularly in a diverse population such as the UK (Fraser et al, 2014), has also not been addressed. Thus, further research as recommended in the Health Technology Assessment review will inform guidelines on the optimum faecal immunochemical test cut-off thresholds and the indications for use of the faecal immunochemical test in clinical practice taking the above variables into account to prevent missed cancers (e.g. still refer to secondary care if faecal haemoglobin is low in a patient who has iron-deficiency anaemia). A risk-score tool may be developed as has been done in Spain, incorporating faecal immunochemical test results with other variables (Cubiella et al, 2016).

Despite the above caveats, there is no doubt that the faecal immunochemical test is a powerful new technology which has the potential to revolutionize referral pathways for suspected colorectal cancer in the future. The sensitivity of the faecal immunochemical test remains extremely high with a summary sensitivity over 90% in both OC-Sensor and HM-JACKarc. It cannot be ignored that it is a cheap (£9 *vs* £368 for a colonoscopy) and non-invasive test that could save the NHS a significant amount of money and improve patient care. While the diagnostic accuracy of the test cannot be expected to be 100% for low risk patients, it remains at present a best guess, extrapolated from data on all comers including high risk patients. Therefore, there is clearly a need for methodologically rigorous, adequately powered, prospective research to not only inform clinicians about the limitations of the faecal immunochemical test, but also about its full potential for both low risk and high risk patients. If planned well and introduced appropriately, patients and GPs will have faith in the test. Consequently, symptomatic patients may be more likely to see their GPs early, knowing that they will undergo a simple accurate test to rule out colorectal cancer instead of the laborious colonoscopy examination that will require bowel preparation and a day off work, leading to early diagnosis.

There are several large diagnostic accuracy studies currently underway in England, some of which are supported by the National Institute of Health Research and funded by NHS England. This research should answer the question about whether the faecal immunochemical test can be used to reliably rule out bowel cancer in England within its diverse population, while also accounting for variables such as age, sex, ethnicity, deprivation and 2-week wait symptoms,

Figure 2. Tumour stage by presentation route. From National Cancer Registration and Analysis Service (2017b).



KEY POINTS

- The faecal immunochemical test is a powerful new technology which is likely to revolutionize the referral pathway for patients with suspected colorectal cancer.
- The evidence for the faecal immunochemical test in low risk patients does not exist and is taken from data on 'all comers' including high risk patients.
- Evidence for the faecal immunochemical test in high risk patients may not necessarily be applicable to patients within England referred on National Institute of Health and Care Excellence 2-week wait guidelines.
- A robust evidence base is needed so that the faecal immunochemical test can be embedded within National Institute of Health and Care Excellence guidelines to its full potential.
- Premature use of the faecal immunochemical test could result in missed cancers.
- If the faecal immunochemical test is to be adopted in patients with low risk symptoms, then rigorous and closely monitored safety netting should be also introduced into clinical pathways.

including low risk symptoms that are still referred in areas such as London. These studies are expected to report their results in the first or second quarters of 2019. The faecal immunochemical test has also been launched as a triage test in high risk patient groups in Nottingham, Leicester and Scotland; the experience of these projects will inform the design of referral and safety netting pathways in England.

Commissioning groups in England are racing to implement DG30 guidance (National Institute for Health and Care Excellence, 2017) in their own localities. The authors would strongly recommend that commissioners plan carefully the logistics for introducing the faecal immunochemical test in their localities to include staff training, developing a business case for procurement and commissioning specifications for pathology as well as establishing well-defined clinical pathways with rigorous and closely monitored safety netting to avoid missing cancers or delayed diagnosis. In addition, to avoid overwhelming endoscopy services with false positives, the authors would recommend that the faecal immunochemical test is used only in the group of patients with low risk symptoms that was originally part of the 2015 NG12 guidance and has since been removed in 2017 following the release of DG30 guidance (National Institute for Health and Care Excellence, 2017) as explained above; an approach supported by Cancer Research UK. Once the large research studies currently underway in England produce their results, the faecal immunochemical test can then be implemented as safely as possible, underpinned by a strong evidence base to achieve its full potential to improve diagnosis and patient care. **BJHM**

Conflict of interest: Mr N D'Souza and Mr M Abulafi are investigators in the NICE FIT Study.

Allison JE, Fraser CG. Fecal immunochemical tests had better sensitivity for detecting colorectal neoplasia in aspirin users than in nonusers. Ann Intern Med. 2011 Apr 19;154(8):JC4–JC10. https://doi.org/10.7326/0003-4819-154-8-201104190-02010

Bowel Cancer UK. 2014. Diagnosing bowel cancer early. Right test, right time. London: Bowel Cancer UK.

Cancer Research UK. 2018. Bowel cancer incidence statistics (accessed 8 December 2018) https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence

Chapman C, Banerjea A, Ng O et al. 2017. 'Getting fit': A comparison of haemoglobin levels as measured by oc-sensor and hm-jackarc. Paper presented at: NCRI Cancer Conferences (accessed 8 December 2018) http://abstracts.ncri.org.uk/abstract/getting-fit-a-comparison-of-haemoglobin-levels-as-measured-by-oc-sensor-and-hm-jackarc/

Cubiella J, Vega P, Salve M, Díaz-Ondina M et al; COLONPREDICT study investigators. Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Med. 2016 Dec;14(1):128. https://doi.org/10.1186/s12916-016-0668-5

Digby J, McDonald PJ, Strachan JA, Libby G, Steele RJC, Fraser CG. Deprivation and faecal haemoglobin: implications for bowel cancer screening. J Med Screen. 2014 Jun;21(2):95–97. https://doi.org/10.1177/0969141314535388

Digby J, Mowat C, Steele R et al. OC-020 Validation of the utility of a faecal immunochemical testfor haemoglobin (fit) in patients presenting to primary care with new bowel symptoms. Gut 2017;66:A10–A11.

Fraser CG. Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: concepts and challenges. Surgeon. 2018 Oct;16(5):302–308. https://doi.org/10.1016/j.surge.2018.01.004

Fraser CG, Rubeca T, Rapi S, Chen LS, Chen HH. Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. Clinical Chemistry and Laboratory Medicine (CCLM). 2014 Jan 1;52(8):1211–1216. https://doi.org/10.1515/cclm-2014-0115

Godber IM, Todd LM, Fraser CG, MacDonald LR, Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. Clinical Chemistry and Laboratory Medicine (CCLM). 2016 Jan 1;54(4):595–602. https://doi.org/10.1515/cclm-2015-0617

National Cancer Intelligence Network. 2015. Routes to diagnosis 2015 update: Colorectal cancer. (accessed 8 December 2018) http://www.ncin.org.uk/publications/routes_to_diagnosis

National Cancer Registration and Analysis Service. 2017a. Routes to diagnosis 2006-2015 workbook. (accessed 8 December 2018) http://www.ncin.org.uk/view?rid=3549

National Cancer Registration and Analysis Service. 2017b. Routes to diagnosis by stage 2012-2013 workbook. (accessed 8 December 2018) http://www.ncin.org.uk/view?rid=3071

National Institute for Health and Clinical Excellence. 2005. Referral guidelines for suspected cancer. Clinical Guidelines 27. (accessed 10 December 2018) https://www.nice.org.uk/guidance/cg27

National Institute for Health and Care Excellence. 2015. Suspected cancer: Recognition and referral. NICE guideline NG12. (accessed 10 December 2018) https://www.nice.org.uk/guidance/ng12

National Institute for Health and Care Excellence. 2017. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. Diagnostics guidance [DG30]. (accessed 8 December 2018) https://www.nice.org.uk/guidance/dg30

NHS England. 2016. Waiting times for suspected and diagnosed cancer patients. 2015-16 annual report. (accessed 8 December 2018) https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2016/06/Cancer-Waiting-Times-Annual-Report-201516-1.pdf

Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJY, Young GP, Kuipers EJ. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015 Oct;64(10):1637–1649. https://doi.org/10.1136/gutjnl-2014-309086

Steele R, Forgacs I, McCreanor G et al. Use of faecal occult blood tests in symptomatic patients. BMJ. 2015 Aug 11;351:h4256. https://doi.org/10.1136/bmj.h4256

Westwood M, Corro Ramos I, Lang S et al. Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017 May;21(33):1–234. https://doi.org/10.3310/hta21330

Widlak MM, Thomas CL, Thomas MG et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017 Jan;45(2):354–363. https://doi.org/10.1111/apt.13865