Review: Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: concepts and challenges.

Callum G Fraser

Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, Scotland

E-mail address: callum.fraser@nhs.net

Sources of financial support: This work had no financial support.

Disclosure of interest: CGF has undertaken paid consultancy with Immunostics Inc., Ocean, NJ, USA, and Kyowa-Medex Co., Ltd, Tokyo, Japan, and has received support to attend conferences from Alpha Labs Ltd, Eastleigh, Hants, UK.

Key words: Bowel disease, Colorectal cancer, Faecal haemoglobin, Faecal immunochemical test, Faecal occult blood test, Inflammatory bowel disease

Short title: FIT in assessment of symptomatic patients.

© 2018. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/
Abstract

Colonoscopy is a relatively scarce resource in many countries, including Scotland, and a simple investigation which would aid general practitioners in particular in decision-making as to which patients presenting with lower bowel symptoms warranted referral would be of much help. Faecal immunochemical tests for haemoglobin (FIT) have many advantageous characteristics and are now proven to be of considerable value in the timely assessment of patients with symptoms of lower bowel disease. Quantitative FIT provide numerical estimates of faecal haemoglobin concentration (f-Hb) and, at low f-Hb cut-off, FIT have high sensitivity for colorectal cancer (CRC) and could be used as a rule-in test to stimulate rapid referral, especially when symptoms are suggestive of serious bowel disease. Perhaps more importantly, a low f-Hb gives considerable reassurance that significant bowel disease (CRC + higher-risk adenoma + inflammatory bowel disease) is absent and further investigation may not be warranted: however, no test is perfect, so some cases will remain undetected using FIT alone and robust safety netting is required, possibly including watching and waiting, referral to clinics in secondary care, or a repeat FIT. Moreover, the FIT results should not be taken in isolation, but clinical impressions and the results of other investigations, probably including the full blood count, should be considered. Challenges still exist, however, and harmonisation of aspects of the available FIT analytical systems is required. Moreover, a number of seemingly valid clinical concerns remain and these require resolution through further research and reporting of studies done in real clinical practice.
Introduction

Colonoscopy is crucial to the early diagnosis of significant bowel disease (SBD), including colorectal cancer (CRC) and inflammatory bowel disease (IBD). Unfortunately, there is evidence, such as that gathered by Bowel Cancer UK, demonstrating that there is a current crisis in endoscopy throughout the UK with services being underfunded, demand outstripping supply, chronic staff shortages and growing waiting lists for investigations.\(^1\) In part, the demand which has led to the increase in referrals from primary care to endoscopy, gastroenterology and surgery in secondary care has been due to the publicity surrounding the bowel screening programmes running in the four countries of the UK and the information that is given to participants with negative screening test results on the need to pay attention to any bowel symptoms and report these as soon as they become apparent. Moreover, campaigns such as Detect Cancer Early in Scotland\(^2\) and Be Clear on Cancer in England\(^3\) have encouraged people with symptoms to make an appointment with their general practitioner (GP) as soon as possible.

Unfortunately, although the symptoms of SBD, namely, repeated rectal bleeding or blood evident on passed faeces, a change in bowel habit that continues for more than four weeks without returning to usual, diarrhoea on its own or with constipation, abdominal pain especially after eating, unexplained loss of weight and tiredness, are very common presentations in primary care; however, these are well documented to be very poor predictors of SBD.\(^4\) Thus, the challenge was to find and then use an investigation that assists the GP to determine which patients with lower bowel symptoms would benefit most from referral to secondary care for colonoscopy. The
primary purpose of this review is to summarise the evidence that faecal immunochemical tests for haemoglobin (FIT) can assist in the triage of these patients and to discuss the challenges that still exist to ubiquitous introduction of FIT as a routine investigation in primary care.

**Faecal immunochemical tests for haemoglobin (FIT)**

Faecal immunochemical tests for haemoglobin (FIT) make use of antibodies, usually polyclonal, to the globin moiety of haemoglobin. Most FIT have simple to use, hygienic faecal specimen collection devices in which a probe attached to the cap of the device is used to collect faeces into dimples or grooves at the end of the probe. Then, the probe is reinserted into the device, which contains a volume of buffer, which confers some stability on any haemoglobin (Hb) present in the faeces. An important point is that these must be used for collection of faecal samples for FIT analysis since faecal haemoglobin (f-Hb) is unstable; collection of faeces into the traditional pot with later analysis can lead to false negative test results. FIT have many positive attributes, including being unaffected by dietary constituents and more specific for lower gastrointestinal bleeding.

FIT are available in two formats. The first is qualitative FIT, which give a dichotomous, positive/negative result, usually using lateral-flow immunochromatographic cassettes or strips, similar to the very widely used pregnancy tests which detect urinary human chorionic gonadotropin (hCG). The disadvantages of qualitative FIT have been very well documented and, since these are not used widely in the UK, this review is mainly concerned with the application of quantitative FIT. Quantitative FIT, usually involving automated
immunoturbidimetry on small bench-top dedicated analytical systems, provide a numerical estimate of the faecal haemoglobin concentration (f-Hb).\(^6\)

**Faecal haemoglobin concentrations (f-Hb)**

Quantitative FIT have become the most widely used non-invasive investigation in both opportunistic and programmatic screening for CRC\(^10\) and much has been learned from the results obtained in screening about f-Hb and the factors that affect f-Hb.\(^11\)

It has been shown that f-Hb is directly related to the severity of colorectal disease.\(^12\) In addition, it has been documented in more detail\(^13\) that median f-Hb is higher in those with CRC than those with no pathology or with minor non-neoplastic pathology. Individuals with low-risk adenoma (LRA), and polyp CRC cancers have lower f-Hb than more advanced stage CRC. Higher f-Hb is also found in those with higher risk adenoma (HRA: three or more polyps, any polyp >10 mm diameter) than with LRA, in large compared with small adenoma, and also in adenoma displaying high-grade dysplasia as compared to those with low-grade dysplasia. Thus, it is hardly surprising that screening the asymptomatic using FIT is very successful.

In addition, in CRC screening programmes, because of this relationship, as the f-Hb cut-off concentration applied to decide which participants are offered colonoscopy is increased, the positivity rate, CRC and adenoma detection rates, and sensitivity decrease, while positive predictive value and specificity increase.\(^14\) Further, as the f-Hb cut-off is increased, the interval cancer proportion, that is the number of CRC found in participants who had a negative screening test result but had a diagnosis of CRC before the next screening episode was scheduled, rises.\(^15\)
Furthermore, a number of factors affect the f-Hb found in different populations: f-Hb is higher in men than in women and increases with age\textsuperscript{16,17} and these relationships differ in magnitude from country to country.\textsuperscript{18} In addition, f-Hb is dependent on deprivation, f-Hb increasing as deprivation increases.\textsuperscript{17,19} In consequence, there is much current interest in using more complex interpretation of the f-Hb of participants in CRC screening than application of one f-Hb cut-off for all to decide on referral for colonoscopy through incorporation of such variables into a risk-score.\textsuperscript{20} In addition, it has been elegantly shown that f-Hb below the cut-off applied in CRC screening is related to the risk of future colorectal disease, particularly if detectable on two occasions.\textsuperscript{21}

**FIT in the assessment of patients presenting with lower bowel symptoms:**

**background**

Even until recently, in spite of the proven relationship between f-Hb and severity of colorectal disease and the successful use of FIT in CRC screening, there was little interest in the application of FIT in the assessment of patients presenting in primary care with lower bowel symptoms. This may have been in part due to the fact that the traditional tests for the presence of blood in faeces, namely, guaiac-based faecal occult blood tests (gFOBT), had many problems and difficulties in all stages of the performance of this apparently simple investigation.\textsuperscript{22} Moreover, older guidelines from the National Institute for Health and Care Excellence (NICE),\textsuperscript{23} the Scottish Intercollegiate Network (SIGN)\textsuperscript{24} and the British Society of Gastroenterology\textsuperscript{25} all stated that gFOBT lacked the clinical characteristics required for the detection of CRC and for the investigation of iron deficiency anaemia. Because of both of these deficiencies, many medical laboratories eliminated gFOBT from their repertoires and
encouraged cessation in all clinical settings such as wards, clinics, surgical admission units and accident and emergency departments.

However, in 2015, the situation changed. NICE issued a revision of Clinical Guideline 27 - Referral guidelines for suspected cancer - published in 2005\textsuperscript{23} as NICE Guideline NG12 - Suspected cancer: recognition and referral.\textsuperscript{26} The guideline concerning lower gastrointestinal cancer stated: 1.3.1. Refer adults using a \{HYPERLINK "https://www.nice.org.uk/guidance/ng12/chapter/terms-used-in-this-guideline"\} (for an appointment within two weeks) for CRC if: they are aged 40 and over with \{HYPERLINK "https://www.nice.org.uk/guidance/ng12/chapter/terms-used-in-this-guideline"\} weight loss and abdominal pain or they are aged 50 and over with unexplained rectal bleeding or they are aged 60 and over with: iron-deficiency anaemia or changes in their bowel habit, or tests show occult blood in their faeces (see Section 1.3.4). Section 1.3.4 followed to detail: Offer testing for occult blood in faeces to assess for CRC in adults without rectal bleeding who: are aged 50 and over with unexplained abdominal pain or weight loss, or are aged under 60 with changes in their bowel habit or iron-deficiency anaemia, or are aged 60 and over and have anaemia even in the absence of iron deficiency.

It is worthy of note that the guidance in Scotland is far less prescriptive. The Scottish referral guidelines for suspected cancer document that high-risk features which warrant urgent suspicion of cancer referral are: repeated rectal bleeding without an obvious anal cause or any blood mixed with the stool, persistent change in bowel habit especially to looser stools (more than 4 weeks), a right-sided abdominal mass or palpable rectal mass, unexplained iron deficiency anaemia and a past history of lower gastrointestinal cancer with any of the symptoms above.\textsuperscript{27} The most recent version of SIGN: Diagnosis and management of CRC. A national clinical guideline.
2011, after revision in 2016, does contain some material on the use of FIT in asymptomatic population screening. However, key point iii still states:

Investigations: No examinations or investigations other than abdominal and rectal examination and full blood count are recommended. Faecal occult blood testing is not indicated and should not influence decision making in symptomatic patients. Thus, the guidelines in England and Scotland are different.

When NICE NG12 was issued, there was considerable negativity expressed. For example, Steele et al stated, inter alia, that the guidance was particularly worrying for people under 60 years with iron deficiency anaemia, that gFOBT should be used only in laboratories with dedicated staff and strict quality assurance and for population screening, and that anyone seeking advice about symptoms wishes reassurance that there is no serious disease but gFOBT is not sufficiently sensitive for this purpose and, because negative tests provide reassurance, diagnosis is likely to be delayed. In response, Hamilton et al responded that half of patients with CRC did not meet the criteria for urgent referral under the previous guidance (CG27) and these patients, who were at low risk but did not have no risk symptoms, did badly, with longer times to diagnosis, more emergency admissions and higher mortality. NG12 sought to improve this and the specific guideline was based on six research papers on faecal occult blood testing (FOBT) in the symptomatic primary care population. Overall, these supported the use of FOBT. However, the response did state that FIT may prove superior to gFOBT when more studies were performed and NG12 deliberately did not actually detail which faecal test should be used.
Similar caveats regarding gFOBT were expressed in the literature of laboratory medicine, it being stated that NG12 was ill-judged and the advice to those responsible for routine clinical biochemistry laboratories was to resist calls to introduce or re-instate gFOBT. However, this editorial did state that, in the future, laboratories might wish to consider offering FIT for the groups detailed in NG12. The rationale available at that time supporting the use of FIT in this clinical context was clearly documented in an editorial published simultaneously, which suggested that professionals in laboratory medicine should take up the challenges of introducing FIT in the assessment of patients presenting in primary care with lower bowel symptoms and work with others in progressing the existing evidence base on this use of f-Hb in assessment of the symptomatic.

In view of the controversy surrounding the recommendations in NG12 to use tests for faecal occult blood and the wide disapproval of the use of gFOBT, NICE set up a Diagnostic Advisory Committee with the remit of investigating the evidence for the use of quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of CRC in primary care. The final Diagnostics Guidance DG30 on quantitative faecal immunochemical tests to guide referral for CRC in primary care was issued in 2017. The major recommendations were that three commercially available quantitative faecal immunochemical test analytical systems were recommended for adoption in primary care to guide referral for suspected CRC in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in the NICE guideline on suspected cancer, NG12, and results should be reported using a threshold of 10 micrograms of haemoglobin per gram of faeces (µg Hb/g faeces). Since the issue of
these guidelines, NG12 has been updated and, in July 2017, the detailed recommendation on use of tests for occult blood in faces (1.3.4 detailed above) was stood down and 1.3.4 became: This recommendation has been replaced by our diagnostics guidance on quantitative faecal immunochemical tests to guide referral for CRC in primary care (DG 30). The diagnostics guidance recommends tests for occult blood in faeces, for people without rectal bleeding but with unexplained symptoms that do not meet the criteria for a suspected cancer pathway referral in recommendations 1.3.1 to 1.3.3. In essence, this tells that it is recommended that GP request a FIT on any patient that is causing concern. The evidence supporting the DG30 recommendations follows in the next section of this review.

**FIT in the assessment of patients presenting with lower bowel symptoms: the evidence**

During and following the generation of NICE NG12 in 2015, a number of peer-reviewed publications were published concerning the use of FIT in assessment of patients presenting with lower bowel symptoms. These have been described in detail in two open-access systematic reviews and in a very recent chapter, which does not only consider quantitative FIT but also details studies using qualitative FIT and also other biomarkers which potentially could supplement clinical data and the results of FIT analysis, including calprotectin and M2-PK, the dimeric form of pyruvate kinase isoenzyme type M2. In consequence, the fine details of these studies will not be documented here. Since the most recent publication, there have only been two further publication concerning the use of quantitative FIT in the assessment of patients with symptoms. One concerns an analytical and clinical
evaluation of a recently available FIT analytical system (SENTiFIT 270, Sentinel Diagnostics, Milan, Italy). Clinical sensitivity for advanced colorectal neoplasia (ACRN: CRC + AN) at f-Hb cut-offs from 10 to 60 μg Hb/g faeces ranged from 28.9% to 46.5% and specificity ranged from 85% to 93.2% (95% CI, 91.2%-94.8%): the positive predictive values (PPV) for detecting CRC and AA ranged from 11.6% to 20.6% and 34.7% to 42.3%, respectively, and the negative predictive values (NPV) ranged from 90.2% to 88.4%. It was concluded that this FIT provided a specific and accurate test for detecting ACRN in symptomatic patients and those undergoing surveillance. Unsurprisingly, using two faecal samples per patient increased clinical sensitivity with a slight decrease in specificity. The second recent publication compared the utility of f-Hb as the initial investigation with the NICE NG12 symptom-based guidelines using data from three studies done in Scotland. The sensitivity and NPV of f-Hb for SBD were 63.2% and 96.0%, respectively. It was concluded that f-Hb provides a good rule-out test for SCD and has significantly higher overall diagnostic accuracy than NG12.

Taken with the other studies using quantitative FIT, exactly as listed in detail previously in the chapter in Timely Diagnosis of Colorectal Cancer, the results provide evidence that demonstrate the following:

- in patients with lower bowel symptoms, f-Hb is higher in those with CRC than in those with advanced adenoma (AA: similar to HRA) and IBD, and f-Hb in these two groups is higher than in those with less significant bowel disease such as non-advanced adenoma (NAA: similar to LRA), haemorrhoids and simple diverticular disease, and those with no abnormalities found on colonoscopy,
• high f-Hb is not only found in patients with SBD, but also in some who have less significant pathology and no abnormality, and so the PPV is not optimal,

• the higher the f-Hb cut-off used for referral for colonoscopy, the lower are the sensitivity, positivity rate and NPV, and the higher the specificity and PPV,

• f-Hb cut-off at the limit of quantitation (LoQ) documented by the manufacturers of the FIT analytical system used should be applied to give highest sensitivity for detection of SBD and highest NPV, albeit at the expense of specificity and PPV,

• at such f-Hb cut-offs, some CRC and some AA and IBD will be missed and safety-netting is mandatory,

• f-Hb provides a good rule-in test for CRC and a patient with a f-Hb above the LoQ should be referred for urgent colonoscopy,

• f-Hb provides a good rule-out test for SBD: a result below the f-Hb cut-off means that SBD is unlikely and many patients can be reassured regarding the absence of disease and not referred immediately, or at all, for colonoscopy,

• f-Hb is better at detection of CRC than some guidelines based upon symptoms, age and other factors for referral from primary care when CRC is suspected,
• one sample is sufficient for detection or exclusion of most SBD,

• men and women with symptoms have different clinical outcomes at a single f-Hb cut-off,

• using two samples from each patient shows that there may be considerable within-subject variation of f-Hb from day to day and this is worthy of further research as has been recently done for faecal calprotectin

• ubiquitous use of f-Hb as the initial investigation in primary care could undoubtedly help direct colonoscopy resources to those who would benefit most.

Thus, the evidence is that the recommendations of NICE DG30 are cogent and application of quantitative FIT in assessment of symptomatic patients would seem to well fulfil the challenge to find and then use an investigation that assists the GP to determine which patients with lower bowel symptoms would benefit most from referral to secondary care for colonoscopy. That this indeed remains a current requirement is evidenced for the findings in the recent major national audit on cancer diagnosis in primary care in England. The audit provided a detailed picture of the timeliness of cancer diagnosis in patients who presented with symptoms. For colon and rectal cancers, the average time it took from first reporting symptoms to a cancer diagnosis was 49 and 42 days respectively. Around 25-30% of patients with colon and rectal cancer waited more than 90 days for a cancer diagnosis. Furthermore,
approximately 30% of patients diagnosed with bowel cancer experienced avoidable delays to their diagnosis.

**FIT in the assessment of patients presenting with lower bowel symptoms: challenges**

Although the evidence is that FIT provide a good test to rule-in CRC and a good test to exclude SBD, there are still a number of challenges.

NICE NG12 suggests that a single f-Hb cut-off of 10 µg Hb/g faeces be used in assessment of patients presenting with symptoms, irrespective of their sex or age, factors well known to affect f-Hb. The publications on FIT\(^{36-43}\) have receiver operating characteristic (ROC) curves and/or tables of clinical performance characteristics at various f-Hb cut-offs: these suggest that 10 µg Hb/g faeces is the most appropriate f-Hb cut-off. Further, the analytical performance characteristics of the available FIT analytical systems are such that a f-Hb cut-off of 10 µg Hb/g faeces is apposite. This approximates to the LoQ of the most used FIT analytical systems. Laboratories providing FIT for triage of the symptomatic must use the LoQ as the lowest limit to give a numerical result and this is 10 µg Hb/g faeces for the OC-Sensor (Eiken Chemical Co., Ltd, Tokyo, Japan) and 7 µg Hb/g faeces for the HM-JACKarc (Kyowa-Medex, Co., Ltd, Tokyo, Japan): concentrations less than this are very interesting from an academic point of view but cannot be simply reported.\(^{11,47}\) LoQ is the lowest concentration at which performance that meets analytical performance specifications is achieved. This is not the same as the limit of detection (LoD), the lowest concentration that is statistically different from a blank (sample with no
haemoglobin present), and the f-Hb above which data can be documented for research and development purposes.\textsuperscript{11,47} It is noteworthy that NICE DG30 documents that: companies should provide advice about the performance characteristics of the assays to laboratories, and ensure standardisation of results.\textsuperscript{32} This is stated because there is considerable evidence that FIT analytical systems do not give identical results on the same faecal samples,\textsuperscript{48} probably due to the fact that polyclonal antibodies to the epitopes on the globin moiety of haemoglobin are used and they react differently to the heterogeneous mix of native haemoglobin and its degradation products present in faeces: this could affect the number of positive and negative results if a single f-Hb cut-off was used. Moreover, faeces is a heterogeneous matrix even in one bowel movement and there is some concern regarding the small specimen collected being representative. There are other analytical challenges and these are currently being addressed by the recently formed Working Group on FIT of the Scientific Division of the International Federation of Clinical Chemistry and Laboratory Medicine.\textsuperscript{49} It is also important to note that manufacturers of FIT do improve their systems over time, an example being the reformulation of the buffers in the specimen collection devices so as to enhance haemoglobin stability.\textsuperscript{50} In consequence, data from older studies using outdated FIT analytical systems or components may not be applicable to those from for newer systems.

More important, perhaps, are the clinical concerns. The first is that the recommendations on the use of FIT in NICE NG12\textsuperscript{26} and DG30\textsuperscript{32} applies only to patients with low risk symptoms. The evidence for this simply does not exist, since the studies done to date,\textsuperscript{36-42} apart from that of Mowat et al\textsuperscript{38} which was performed in
primary care, were concerned with patients who had already been referred to secondary care and were not only concerned with patients with low risk symptoms. Further work on this interesting group is required as soon as possible. In reality, it is highly likely that GP will request a FIT on all patients presenting with lower bowel symptoms and this can be justified on the grounds that symptoms in SBD and other bowel disorders overlap considerably. However, it might be considered that there may be good grounds for fast-tracking those with the symptoms and signs as documented requiring urgent referral in current NICE NG12\textsuperscript{26} and HIS\textsuperscript{27} guidance, irrespective of the FIT result: again this is a facet of the use of FIT in assessment of the symptomatic which requires objective investigation.

The second problem is that, to date, there are no peer-reviewed publications on the application of FIT in real practice. NICE recommend that commissioning groups adopting the endorsed FIT analytical systems should audit their outcomes and monitor the associated resource use.\textsuperscript{32} Again, it would be of real interest to see such audits of outcomes performed and the results promulgated to all healthcare professionals involved in the use of FIT and to have lessons learned in the implementation of FIT also well documented and disseminated. Further, it has been stated that use of FIT by GP might actually increase the number of referrals for colonoscopy since they will request this investigation on every patient presenting with lower bowel symptoms and, since the PPV is low, many with false positive FIT results will be referred to secondary care: again, research into the results attained in real practice is required.
Thirdly, the recommendation in NICE DG30 was that the f-Hb cut-off of 10 µg Hb/g faeces should be applied ubiquitously, although it was considered that further research was needed to determine whether f-Hb are influenced by age, sex and medicines that increase the risk of gastrointestinal bleeding. It was noted that such data could be used to further develop risk scores which include variables such as age, sex and symptoms to help determine pre-test probability. Such risk scoring approaches do exist and have been recently reviewed. Only a few of the models suggested incorporate f-Hb, examples being the COLONPREDICT approach and the FAST Score developed with much input from research centres in Scotland: their application in routine clinical care has not yet been established.

Fourthly, it must be realised that no test in laboratory medicine is perfect. Using the f-Hb cut-off of 10 µg Hb/g faeces a few cases of CRC will be missed and rather more cases of HRA and IBD. Thus, there is a real need for robust safety netting as described above, which would not only include watching and waiting but might also involve referral to gastroenterology or surgery clinical in secondary care or undertaking a repeat FIT. Moreover, it is vital to note that the FIT results should not be viewed in isolation but clinical judgement on the individual patient and the results of physical examinations and the full blood count should be taken into account.

Conclusions

FIT are now proven to be very useful in the timely assessment of patients with symptoms of lower bowel disease. In particular, FIT can guide in the decision-making as to which patients presenting in primary care with lower bowel symptoms would most benefit from referral for colonoscopy. Quantitative FIT provide numerical
estimates of f-Hb and, at low f-Hb cut-off, FIT have high sensitivity for colorectal cancer (CRC) and could be used as a rule-in test and stimulate rapid referral, especially when symptoms are suggestive of serious bowel disease. Perhaps more importantly, low f-Hb provides considerable reassurance that significant bowel disease is absent and further investigation may not be required: however, no test is perfect so some cases will remain undetected and robust safety netting is required, including, for example, watching and waiting, referral to appropriate clinics in secondary care, or a repeat FIT. In addition, the FIT results should not be taken in isolation but clinical impressions and the results of other investigations, probably including the full blood count, should be considered. Challenges still exist, however, and harmonisation of aspects of the available FIT analytical system is required. Moreover, a number of valid clinical concerns remain and these require resolution. Thus, although there is considerable positive evidence regarding the use of FIT in assessment of patients presenting in primary care with lower bowel symptoms, there is still much of importance to learn about the application in everyday clinical practice which can only be ascertained when this test is introduced and the results in this setting are generated and subsequently widely disseminated.

References


3. https://www.nhs.uk/be-clear-on-cancer/symptoms/bowel-cancer#fKRhgRcByc7aMuk0.97


