Anaemia as a risk stratification tool for symptomatic patients referred via the two-week wait pathway for colorectal cancer

S Mashlab¹, P Large¹, W Laing¹, O Ng¹, M D'Auria¹, D Thurston¹, S Thomson¹, AG Acheson¹, DJ Humes², A Banerjee¹, On behalf of the Nottingham Colorectal Service*

¹Nottingham University Hospitals NHS Trust, UK

²NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK

ABSTRACT

INTRODUCTION Anaemia is associated with cancer. In 2014 a new form was introduced in our department requesting a haemoglobin (Hb) result on every two-week wait referral for suspected colorectal cancer (CRC). The aim of this study was to review the impact of this intervention. In particular, the significance of any evidence of anaemia (without additional indices) was investigated.

METHODS A review was conducted of 1,500 consecutive suspected CRC referrals recorded prospectively over a 10-month period. Data on demographics, referral Hb, referral criteria and outcomes were analysed. Anaemia was defined according to World Health Organization criteria (Hb <120g/l for women, Hb <130g/l for men).

RESULTS Overall, 1,015 patients were eligible for inclusion in the study. Over a third (38.2%) were documented as anaemic on referral. These patients were three times more likely to be diagnosed with CRC than non-anaemic patients (odds ratio [OR]: 3.22, 95% confidence interval [CI]: 1.87–5.57). Using a more stringent threshold (Hb <100g/l for women and <110g/l for men), they were four times more likely to have CRC (OR: 4.27, 95% CI: 2.35–7.75). Almost a quarter (23.7%) were actually anaemic at the time of referral but not referred with anaemia. In this subgroup, there was a 2.8-fold increase in risk of CRC diagnosis compared with non-anaemic patients (adjusted OR: 2.77, 95% CI: 1.55–4.95).

CONCLUSIONS Nearly a quarter of patients not referred with iron deficiency anaemia had evidence of anaemia and this was still associated with a higher rate of CRC detection. A full blood count alone might help to risk stratify symptoms such as change in bowel habit in patients on urgent pathways and identify those cases most likely to benefit from invasive investigation.

KEYWORDS

Colorectal cancer – Anaemia – Iron deficiency – Diagnostics

Accepted 16 October 2017

CORRESPONDENCE TO

Samer Mashlab, E: samer.mashlab@nhs.net

Colorectal cancer (CRC) is common, with over 41,000 new diagnoses made annually in the UK.¹ In 2000 guidelines for urgent referral on a two-week wait (2WW) pathway were introduced, the aim being early diagnosis by promoting rapid assessment and investigation.² Despite this, the cancer detection rate within this pathway has stayed stubbornly below 10% among those referred and just as many cancers are diagnosed in those referred via routine pathways.^{3–6} Approximately, a third of patients referred via this pathway have no detectable pathology and another third have no pathology that mandates intervention or treatment. In 2015 new National Institute for Health and Care Excellence (NICE) guidance updated and broadened the

referral criteria, with a benchmark for investigation of any symptom with a positive predictive value for cancer of >5%.⁷

Colonoscopy remains the 'gold standard' for whole colon investigation but it is expensive and invasive, with recognised complications. The pressure on endoscopy services is growing to unsustainable levels. The financial burden on the National Health Service (NHS) and the 2015 *Montgomery v Lanarkshire Health Board* judgement⁸ must surely warrant a review of the appropriateness and cost effectiveness of less invasive methods. Flexible sigmoidoscopy⁹ and computed tomography (CT) colonography¹⁰ present obvious alternatives but they should ideally be performed

*Non-author contributors: J Abercrombie, S Asgari, B Bharathan, R Briggs, H Edis, C Maxwell-Armstrong, K Mohiuddin, M Robinson, J Scholefield, K Thomas, K Walter, J Williams

in the context of safe and reliable risk stratification within the 2WW pathway.¹¹

Iron deficiency anaemia (IDA) has been a criterion for referral on the colorectal 2WW pathway since inception because of its association with occult gastrointestinal (GI) bleeding from neoplastic lesions.¹² The stringency of thresholds for referral in IDA was relaxed in the 2015 NICE guidance.⁷ IDA is recognised to have a high predictive value, and is commonly investigated with upper and lower GI endoscopy.¹⁵ 2WW referrals often do not include all of the indices required to determine the nature of a patient's anaemia and decisions to investigate were frequently made without this information in our service previously.

The significance of anaemia in diagnosing CRC has been highlighted mainly in primary care studies.^{14–18} However, secondary care studies have noted concerns over the referral of cases without evidence of iron deficiency while recognising that the previous cut-off levels in the 2005 guidelines might have been too stringent.^{19,20} The presence of anaemia in patients with rectal bleeding is recognised as a risk factor in the 2015 NICE guidance⁷ but its value in cases referred with other symptoms is less clear.

In 2014 a 'straight to test' (STT) colonoscopy pathway was implemented in our department to reduce the time to diagnosis in our 2WW pathway.²¹ This was developed in conjunction with local clinical commissioning groups and general practitioners, and a new referral form was introduced that required additional patient information including results for haemoglobin (Hb), mean corpuscular volume and ferritin for every referral. It was agreed that a request for blood tests at the time of referral would also suffice. In fact, no referrals were rejected or returned even when this was not adhered to. The aim of this study was to review the impact of this intervention in a series of consecutive colorectal 2WW referrals received at our trust. In particular, the significance of any evidence of anaemia (without additional indices) was investigated.

Methods

Adults referred to the colorectal service at Nottingham University Hospitals NHS Trust under the 2WW pathway for CRC are recorded prospectively on a local database in accordance with best practice guidance. The name, date of birth, age, sex, hospital ID number, NHS number, date of referral and indication for referral are recorded for each patient. All referrals are screened by specialist nurses and vetted with a consultant colorectal surgeon to determine whether the STT pathway, an outpatient clinic appointment with a nurse specialist or consultant, or diversion of the referral is the most appropriate. Following this, the nurse has a telephone consultation with the patient to ensure that he or she is suitable for the pathway chosen. All cases referred under the 2WW pathway between 1 December 2014 and 9 October 2015 for suspected CRC were reviewed.

Data for Hb and ferritin at the time of referral were collected retrospectively from the hospital electronic reporting system. Investigations instigated from the referral review (either STT or outpatient appointment) were endoscopic

(colonoscopy, flexible sigmoidoscopy or gastroscopy), radiological (CT of the abdomen and pelvis, CT of the chest, abdomen and pelvis or CT colonography), a combination of both, or there were no investigations after discussion with the patient or because of patient non-attendance. Investigation reports, cancer diagnosis and outcome were obtained from the hospital electronic reporting system.

Cohort

All patients referred under the 2WW pathway for suspected CRC were identified from the referral database created by specialist nurses at the colorectal service. Duplicate and rejected referrals were excluded, as were cases with no full blood count (FBC) on referral, no investigations or an unknown outcome.

The most recent Hb measurement at the point of referral was used to determine anaemia. Patients were considered to be anaemic if their Hb was <120g/l or <130g/l for women and men respectively, as defined by the World Health Organization (WHO).²² In this paper, anaemia refers to unclassified anaemia (including IDA, non-IDA and anaemia where the distinction could not be made). Where specified, IDA was defined as proposed by the British Society of Gastroenterology (ferritin <50µg/l in the presence of anaemia).²³ Patients with a referral criterion of IDA were considered as one group, irrespective of whether they had other symptoms. The presence of unclassified anaemia was ascertained for all referred cases. Age was categorised as 18–49, 50–59, 60–69, 70–79 or ≥80 years.

Outcome definition

CRC diagnosis was determined from investigation outcome. Evidence of lower GI malignancy on colonoscopy and histology reports confirming adenocarcinomas were reviewed for diagnosis. Cancers other than CRC and benign diagnoses were not the focus of this study.

Statistical analysis

Data were assessed for normality using histograms and a Shapiro–Wilk test. Comparisons were made between continuous variables using the Student's t-test if normally distributed or the Mann–Whitney U test if not normally distributed. Categorical data were summarised using frequencies and percentages. Missing data were classified in a separate category and included in models. Comparisons were made between categorical data using chi-squared tests. Logistic regression analysis was used to test the association between diagnosis of CRC and anaemia, accounting for age and sex. All statistical analysis was performed using Stata® version 14 (StataCorp, College Station, TX, US). A *p*-value of <0.05 was considered statistically significant.

Results

A total of 1,500 referrals under the 2WW pathway for suspected CRC were reviewed. Twenty-eight duplicate referrals were excluded. Two referrals were diverted: one patient had signs and symptoms appropriate for the upper

GI pathway, and a second case was deemed medical and referred to the gastroenterology team. These two patients were excluded from analysis.

Referrals for 334 patients (22.3%) had no Hb at referral. Ten (3%) of these had a ferritin measurement only with seven of these ten having low ferritin. Seventeen of the patients with no Hb at referral (5.1%) were actually referred with IDA. However, only three had a ferritin level

(all <50µg/l). Among the cases with no Hb at referral, there were ten diagnoses of CRC (3.0%). Two of these were referred with IDA with no blood results to confirm this. The 334 referrals with no HB were not included in subsequent analysis. A further 121 referrals (8.1%) were excluded from the study as they had no investigation and therefore an unknown outcome. Consequently, 1,015 patients were selected for further data analysis (Fig 1).

Figure 1 Flow diagram showing total number of cohort, anaemic patients and subgroups

Table 1 Demographics of patients referred via the two-week wait pathway		
	Anaemic (n=388)	Non-anaemic (n=627)
Median age in years	75 (IQR: 67.5–83)	66 (IQR: 56–75)
0–49 years	15 (3.9%)	85 (13.6%)
50–59 years	37 (9.5%)	118 (18.8%)
60–69 years	66 (17.0%)	182 (29.0%)
70–79 years	134 (34.5%)	172 (27.4%)
≥80 years	136 (35.1%)	70 (11.2%)
Sex		
Male	173 (44.6%)	288 (45.9%)
Female	215 (55.4%)	339 (54.1%)
IQR = interquartile range		

Patient demographics and anaemia

The median patient age was 70 years (interquartile range [IQR]: 59–77 years) and 45.4% (461/1,015) were men. In total, 38.2% (388/1,015) were anaemic according to the WHO criteria. The median age of the anaemic patients was greater than that of the non-anaemic patients (75 years [IQR: 67.5–83 years] vs 66 years [IQR: 56–75 years], $p=0.0001$). There was no significant difference in the proportion of men and women in the anaemic and non-anaemic groups (Table 1). A fifth of patients (20.3%, 206/1,015) were referred with IDA but only just over half of these cases (56.8%, 117/206) had evidence of IDA. In this group, the proportion of female patients was greater (62.4%, 73/117) and the median age was 73 years (IQR: 67–81 years).

Investigations and outcomes

A breakdown of the different tests requested is given in Table 2. Over half of the total cohort (58.6%, 595/1,015) had a colonoscopy only and a fifth in this group (20.7%, 123/595) were anaemic. A total of 75 cancers were

Table 2 First diagnostic test performed in patients referred via the two-week wait pathway		
Investigation	Anaemic (n=388)	Non-anaemic (n=627)
Colonoscopy	123 (31.7%)	472 (75.3%)
Colonoscopy and CT	14 (3.6%)	21 (3.3%)
CT	84 (21.6%)	54 (8.6%)
OGD and colonoscopy/sigmoidoscopy	115 (29.6%)	28 (4.5%)
OGD and CT	7 (1.8%)	0 (0%)
Sigmoidoscopy	34 (8.8%)	43 (6.9%)
Other	11 (2.8%)	9 (1.4%)
CT = computed tomography; OGD = oesophagogastroduodenoscopy		

diagnosed: 60 cases of CRC (5.9%) and 15 other cancers (1.5%). Polyps (10.6%) and diverticular disease (9.8%) were the two most common outcomes for benign disease. Haemorrhoids (7.4%), colitis (4.1%) and ‘other’ diagnoses (5.8%) completed the non-malignant outcomes. Over half of the patients (56.0%, 568/1,015) did not have an identifiable cause for their symptoms and a third in this group (36.3%, 206/568) were anaemic at referral (Table 3). Two-thirds of these anaemic patients (62.1%, 128/206) had a ferritin level at referral, with two-thirds being abnormally low (65.6%, 84/128).

Colorectal cancer and anaemia

Anaemia was evident in 68.0% (51/75) of all cancers. In this group, only 51.0% (26/51) had a ferritin level, with 76.9% of these cases (20/26) having low ferritin. Men were more likely to be diagnosed with CRC than women (8.0% [37/461] vs 4.2% [23/554], $\chi^2=6.8$, $p=0.009$). In patients with CRC, 65.0% (39/60) had anaemia. Almost half of these (48.7%, 19/39) had a ferritin level, with 89.5% (17/19) having an abnormally low result at the time of referral. Patients with anaemia were more likely to have a diagnosis

Table 3 Diagnosis following investigation of patients with unclassified anaemia versus non-anaemic patients referred via the two-week wait pathway		
Diagnosis	Anaemic (n=388)	Non-anaemic (n=627)
Colorectal cancer	39 (10.1%)	21 (3.3%)
Other cancer	12 (3.1%)	3 (0.5%)
Diverticular disease (with/without haemorrhoids)	35 (9.0%)	65 (10.4%)
Polyps	33 (8.5%)	75 (12.0%)
Haemorrhoids (without diverticular disease)	17 (4.4%)	46 (7.3%)
Colitis	11 (2.8%)	31 (4.9%)
Other	35 (9.0%)	24 (3.8%)
None	206 (53.1%)	362 (57.7%)

of CRC than those who were not anaemic (65.0% [39/60] vs 35.0% [21/60], $\chi^2=19.4$, $p=0.001$). Forty-one cases of CRC (68.3%) were left-sided and eighteen (30.0%) were right-sided (with 17 of these [94.4%] having anaemia). One patient (1.7%) had synchronous CRC. In patients found to be anaemic on referral, only 60.1% (233/388) had also had ferritin levels measured at the time of referral.

Anaemia and other referral symptoms

Among the 206 patients whose referral included IDA as a criterion, 127 (12.5% of total cohort) were referred with IDA alone while 79 (7.8%) were referred with IDA and other symptoms. In the latter group, change in bowel habit (CIBH) and CIBH with rectal bleeding were the most common symptom (43.0% [436/1,015] and 16.6% [168/1,015] respectively). A quarter of those with CIBH alone (25.0%, 109/436) had anaemia compared with a tenth of those with CIBH and rectal bleeding (10.7%, 18/168).

In those not referred with IDA, 23.7% (192/809) actually had anaemia. In this group, those with anaemia were more likely to be diagnosed with CRC than those without (8.9% [17/192] vs 3.4% [21/617], $\chi^2=9.7$, $p=0.001$). In patients referred with CIBH, those with anaemia were also more likely to have a CRC diagnosis (8.3% [9/109] vs 1.8% [6/327], $\chi^2=10.1$, $p=0.001$) (Table 4).

Association of anaemia at referral and colorectal cancer diagnosis

Anaemia at referral was associated with a 3.2-fold increase in risk of diagnosis of CRC compared with patients without anaemia at referral (unadjusted odds ratio [OR]: 3.22, 95% confidence interval [CI]: 1.87–5.57). When accounting for the confounding effects of age and sex, this relationship weakened slightly to a 2.8-fold increase (adjusted OR: 2.77, 95% CI: 1.55–4.95). When a lower threshold for anaemia was used (Hb 100g/l for women and 110g/l for men), this association strengthened (adjusted OR: 4.27, 95% CI: 2.35–7.75). For those patients referred by the general practitioner specifically for IDA on the initial 2WW proforma ($n=200$), there was a 1.8-fold increase in risk of diagnosis

of CRC compared with patients referred with other symptoms when accounting for age and sex (adjusted OR: 1.83, 95% CI: 1.02–3.27).

Discussion

These data demonstrate that anaemia (with or without evidence of iron deficiency) in symptomatic patients referred via the 2WW pathway for suspected CRC indicates an approximately three-fold increase in the likelihood of CRC diagnosis compared with those who are not anaemic. Clearly, this has value in deciding which cases are most likely to benefit from colonoscopy and which might be better investigated with CT colonography or flexible sigmoidoscopy as a first test. Interestingly, in our study, anaemia was a stronger predictor of increased risk than actual referral with IDA (adjusted OR: 2.8 vs 1.8). However, the group with anaemia obviously contains patients with unidentified or early iron deficiency and some patients in this cohort might have had anaemia corrected in primary care.

Importantly, evidence of anaemia was associated with a higher rate of CRC detection in those referred with CIBH and CIBH without anaemia had a predictive value of <3% in our cohort (Table 4). All but one of the patients with right-sided cancer had anaemia or a synchronous left-sided lesion. We propose that every 2WW referral should include a Hb result or a FBC request at the very least. This cohort is selective (chosen for urgent referral by our colleagues in primary care) and it is not proposed that all individuals with anaemia should be referred for investigation. Nevertheless, the significance of anaemia in cases with other symptoms suggestive of CRC is perhaps underestimated in the secondary care setting and waiting for ferritin results when they are not initially available may not be valuable.

In a retrospective study, it is difficult to distinguish those patients who were anaemic (iron deficient or otherwise) and completely asymptomatic from those who had anaemia with symptoms. However, in our cohort, a substantial proportion of patients referred for other symptoms were in

Table 4 Indication for referral in patients not referred with iron deficiency anaemia				
Indication for referral	Anaemic		Not anaemic	
	Total	CRC	Total	CRC
CIBH ($n=436$)	109	9 (8.3%)	327	6 (1.8%)
Rectal bleeding ($n=113$)	36	3 (8.3%)	77	3 (3.9%)
CIBH with rectal bleeding ($n=168$)	18	1 (5.6%)	150	7 (4.7%)
Rectal mass ($n=31$)	9	3 (33.3%)	22	4 (18.1%)
Abdominal mass ($n=29$)	10	1 (10.0%)	19	1 (5.3%)
Other* ($n=32$)	10	0 (0%)	22	0 (0%)
Total ($n=809$)	192	17 (8.9%)	617	21 (3.4%)
CIBH = change in bowel habit; CRC = colorectal cancer				
*includes weight loss and abnormal radiology				

fact anaemic (23.7%, 192/809) and nearly a quarter of these had evidence of iron deficiency (24.4%, 47/192). It should be highlighted that despite our new form mandating a Hb measurement, more than a fifth of referrals were received without FBC results and ten cancers were diagnosed in this group. These missing data might confound our results. On the other hand, the CRC detection rate for these cases (3.0%) mirrors that in our non-anaemic group (3.3%).

IDA is amenable to therapy with several modalities and this is particularly important as preoperative anaemia is strongly linked with higher morbidity and mortality following surgery. It has been shown that preoperative Hb $\leq 100\text{g/l}$ is associated with a significant increase in perioperative mortality in patients undergoing non-cardiac surgery.²⁴ Furthermore, poor oncological outcomes have been observed after perioperative blood transfusion.^{25,26} Anaemia has also been associated with poor response to neoadjuvant chemoradiotherapy in rectal cancer.²⁷ Early identification and intervention to address a potentially reversible risk factor must therefore be considered best practice²⁸ although it is acknowledged that not all CRC responds to therapy.²⁹

The cost of diagnostics in the 2WW pathway for CRC is enormous, and the majority of patients endure the anxiety and discomfort of invasive investigation without any treatable pathology identified. There is clearly a need to stratify risk in this pathway to improve clinical effectiveness.¹¹ Such stratification could help to choose which test patients should undergo.

The value of IDA as an indicator for whole colon investigation has been well described,¹⁵ as has the value of combinations of other symptoms.³⁰ However, the relevance of any anaemia in combination with other symptoms has been ignored in secondary care models, which focus more on the nature of symptoms,¹¹ although it does feature in primary care scoring systems such as QCancer[®],¹⁵ BB (Bristol-Birmingham) equation¹⁶ and the CAPER (Cancer Prediction in Exeter) score.¹⁷ Our data suggest that including anaemia in secondary care risk stratification could be valuable, particularly if combined with newer diagnostic aids such as quantitative occult blood testing using the faecal immunochemical test (FIT).³¹

Our study period mostly precedes the publication of the new NICE guidance on urgent cancer referral in June 2015.⁷ These guidelines broadened the range of cases to be referred and increased the pressure on secondary care services. Interestingly, they highlight the significance of IDA in young patients with rectal bleeding but not in patients with CIBH.

NICE also opened the door for faecal occult blood testing, including in patients aged <60 years with any type of anaemia, without defining which test should be used. This drew criticism because of concerns around the guaiac-based faecal occult blood test (which has been withdrawn as a diagnostic test for symptomatic patients in our service) and many others because of poor sensitivity despite it being the mainstay of the Bowel Cancer Screening Project. Subsequently, the Bowel Cancer Screening Project made the decision to switch to FIT³² but there is ongoing debate

regarding appropriate cut-off levels for a much more sensitive test and the resource implications that follow. NICE has reviewed limited evidence on FIT for symptomatic patients and has tentatively recommended a cut-off value of $10\mu\text{g}$ of Hb per gram of faeces.³⁵

UK studies have reported the huge potential of FIT as a 'rule-out' test in CRC but uncertainty surrounds the threshold at which cancer can safely be excluded, with the Dundee group having to adjust its cut-off value for positivity to a lower level than planned initially.^{34,35} Furthermore, a Scandinavian study of 373 patients suggested that a combination of FIT and Hb concentration might yield enhanced diagnostic performance for significant bowel disease.³⁶ The FAST score (combining faecal Hb, age and sex) holds great promise³¹ but our data suggest that it could be developed further by including anaemia.

Clearly, if urgent referral pathways are to produce better clinical outcomes, the system must promote diagnosis at an earlier stage and allow optimisation of all potentially reversible risk factors. Our 2WW pathway now aims to identify anaemia at referral in order to improve on both of these measures. Importantly, anaemia could be used as a risk stratification tool to select lower risk patients for CT colonography and flexible sigmoidoscopy instead of colonoscopy. This could reduce the need for double investigation with subsequent endoscopy and biopsy in those with abnormal first tests without increasing the risk of missed diagnosis.

Unfortunately, almost a quarter of referrals are still sent with no information on FBC. The introduction of the electronic referral service might present an opportunity to make FBC (and other blood test) results or requests mandatory. In conjunction with our local commissioners and colleagues in primary care, we are currently exploring new algorithms based on local data to ensure a Hb value is considered for every referral so that the clinical effectiveness of our 2WW pathway can be improved.

Conclusions

Nearly a quarter of patients not referred with IDA had evidence of anaemia and this was still associated with a higher rate of CRC detection. A full blood count alone might help to risk stratify symptoms such as CIBH in patients on urgent pathways and identify those cases most likely to benefit from invasive investigation.

Conflicts of interest

AB and ON are joint directors of Nuhcleus Ltd, which provides software currently used for data collection and management. This software was not in use during the study period. The research department of AGA has received grant support from Syner-Med (UK), Vifor Pharma (Switzerland) and Pharmacosmos (Denmark). AGA has received honoraria and travel support for consulting or lecturing from Ethicon Endo-Surgery (UK), Johnson & Johnson (UK), Olympus (UK) and Vifor Pharma (Switzerland).

Acknowledgements

The authors would like to thank Dr Nina Lewis and the Department of Gastroenterology as well as the Nottingham City Hospital Endoscopy Service and Department of Radiology at Nottingham University Hospitals NHS Trust for help in conducting this study.

References

1. Cancer Research UK. Bowel Cancer Incidence Statistics. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/> (cited January 2018).
2. Department of Health. *The NHS Cancer Plan*. London: DH; 2000.
3. Leung E, Grainger J, Bandia N, Wong L. The effectiveness of the '2-week wait' referral service for colorectal cancer. *Int J Clin Pract* 2010; **64**: 1,671–1,674.
4. Thorne K, Hutchings HA, Elwyn G. The effects of the Two-Week Rule on NHS colorectal cancer diagnostic services: a systematic literature review. *BMC Health Serv Res* 2006; **6**: 43.
5. Chohan DP, Goodwin K, Wilkinson S *et al*. How has the 'two-week wait' rule affected the presentation of colorectal cancer? *Colorectal Dis* 2005; **7**: 450–453.
6. Debnath D, Dielehner N, Gunning KA. Guidelines, compliance, and effectiveness: a 12 months' audit in an acute district general healthcare trust on the two week rule for suspected colorectal cancer. *Postgrad Med J* 2002; **78**: 748–751.
7. National Institute for Health and Care Excellence. *Suspected Cancer: Recognition and Referral*. London: NICE; 2015.
8. Montgomery v Lanarkshire Health Board [2015] UKSC 11.
9. Thompson MR, Flashman KG, Wooldrage K *et al*. Flexible sigmoidoscopy and whole colonic imaging in the diagnosis of cancer in patients with colorectal symptoms. *Br J Surg* 2008; **95**: 1,140–1,146.
10. Atkin W, Dadswell E, Wooldrage K *et al*. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013; **381**: 1,194–1,202.
11. Williams TG, Cubiella J, Griffin SJ *et al*. Risk prediction models for colorectal cancer in people with symptoms: a systematic review. *BMC Gastroenterol* 2016; **16**: 63.
12. National Institute for Health and Clinical Excellence. Anaemia – Iron Deficiency. <https://cks.nice.org.uk/anaemia-iron-deficiency/#scenario> (cited January 2018).
13. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1,309–1,316.
14. Hamilton W, Green T, Martins T *et al*. Evaluation of risk assessment tools for suspected cancer in general practice: a cohort study. *Br J Gen Pract* 2013; **63**: e30–e36.
15. Hippisley-Cox J, Coupland C. Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract* 2012; **62**: e29–e37.
16. Marshall T, Lancashire R, Sharp D *et al*. The diagnostic performance of scoring systems to identify symptomatic colorectal cancer compared to current referral guidance. *Gut* 2011; **60**: 1,242–1,248.
17. Hamilton W. The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients. *Br J Cancer* 2009; **101**(Suppl 2): S80–S86.
18. Hamilton W, Lancashire R, Sharp D *et al*. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. *Br J Cancer* 2008; **98**: 323–327.
19. Shaw AG, Simpson J, Tierney G *et al*. Referral of patients with iron deficiency anaemia under the lower gastrointestinal two-week wait rule. *Colorectal Dis* 2008; **10**: 294–297.
20. Masson S, Chinn DJ, Tabaqchali MA *et al*. Is anaemia relevant in the referral and diagnosis of colorectal cancer? *Colorectal Dis* 2007; **9**: 736–739.
21. Banerjee A, Voll J, Chowdhury A *et al*. Straight-to-test colonoscopy for 2-week wait referrals improves time to diagnosis of colorectal cancer and is feasible in a high-volume unit. *Colorectal Dis* 2017; **19**: 819–826.
22. World Health Organization. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity*. Geneva: WHO; 2011.
23. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1,309–1,316.
24. Carson JL, Duff A, Poses RM *et al*. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1,055–1,060.
25. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg* 2012; **256**: 235–244.
26. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006; **1**: CD005033.
27. Walter CJ, Bell LT, Parsons SR *et al*. Prevalence and significance of anaemia in patients receiving long-course neoadjuvant chemoradiotherapy for rectal carcinoma. *Colorectal Dis* 2013; **15**: 52–56.
28. Keeler BD, Simpson JA, Ng O *et al*. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. *Br J Surg* 2017; **104**: 214–221.
29. Keeler BD, Mishra A, Stavrou CL *et al*. A cohort investigation of anaemia, treatment and the use of allogeneic blood transfusion in colorectal cancer surgery. *Ann Med Surg* 2015; **6**: 6–11.
30. Thompson MR, Perera R, Senapati A, Dodds S. Predictive value of common symptom combinations in diagnosing colorectal cancer. *Br J Surg* 2007; **94**: 1,260–1,265.
31. Cubiella J, Digby J, Rodríguez-Alonso L *et al*. The fecal hemoglobin concentration, age and sex test score: development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients. *Int J Cancer* 2017; **140**: 2,201–2,211.
32. GOV.UK. We're Getting FIT for Bowel Cancer Screening. <https://phescreening.blog.gov.uk/2016/07/25/were-getting-fit-for-bowel-cancer-screening/> (cited January 2018).
33. National Institute for Health and Care Excellence. *Quantitative Faecal Immunochemical Tests to Guide Referral for Colorectal Cancer in Primary Care*. London: NICE; 2017.
34. 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; **45**: 354–363.
35. Mowat C, Digby J, Strachan JA *et al*. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. *Gut* 2016; **65**: 1,463–1,469.
36. Högberg C, Karling P, Rutegård J, Lilja M. Diagnosing colorectal cancer and inflammatory bowel disease in primary care: the usefulness of tests for faecal haemoglobin, faecal calprotectin, anaemia and iron deficiency. A prospective study. *Scand J Gastroenterol* 2017; **52**: 69–75.