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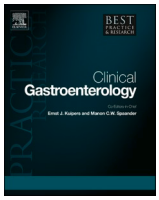

# Colorectal cancer in symptomatic patients: How to improve the diagnostic pathway

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ABSTRACT

Even in countries with national screening programmes for colorectal cancer, most cancers are identified after the patient has developed symptoms. The patients present these symptoms usually to primary care, or in some countries to specialist care. In either healthcare setting, the clinician has to consider cancer to be a possibility, then to perform triage investigations, followed by definitive investigation, usually by colonoscopy. This apparently simple pathway is not simple: most symptoms of colorectal cancer are more likely to represent benign disease than cancer, and each of these stages represents selection of patients into a higher-risk pool. This article summarises a symptom-based approach to selection and initial investigation of such patients in primary care. Some special groups need particular attention, including the younger patient, those with an inherited predisposition to cancer, and those with co-morbidities.

## 1. Introduction

The main pathway to diagnosis for colorectal cancer is following a symptomatic presentation, either in primary care, or direct to specialist. Thus, improving the symptomatic pathway is key to improving patient outcomes and survival. Achieving improvement in the pathway requires a multifaceted approach, including increasing awareness of the disease in the public, optimizing triage strategies in primary care, and improving access to diagnostic tests.

## 2. The benefits of expedited symptomatic colorectal cancer diagnosis

It is largely accepted that expedited diagnosis of symptomatic cancer yields benefits. These are generally considered from the aspect of improved survival, though morbidity benefits may also accrue. These mortality benefits include reduced psychological distress, often less onerous treatment (with fewer side-effects) and sometimes less extensive surgery. There are also cost-benefits, arising from reduced treatment, though this ignores any extra costs of the enhanced diagnostic services needed to expedite the diagnosis [1].

A systematic review published in 2015 concluded that shorter time to diagnosis in colorectal cancer is generally associated with better patient outcomes [2]. However, most of the papers in that systematic review were observational studies, largely because randomized trials in the diagnostic arena require very large numbers, and are expensive. They also raise ethical problems, as by their very nature those not receiving an intervention may receive a slowed diagnosis. Many of the studies in the systematic review showed a U-shaped curve, with worse survival for both short times to diagnosis and for long times to diagnosis, and the best survival for times to diagnosis near the median time to diagnosis – which was usually around a month. This phenomenon of worse survival in those diagnosed rapidly, the 'waiting time paradox', was explored further in a large analysis of six international datasets of colorectal cancer diagnosis. The poorer survival with short diagnostic intervals was considered to represent the very ill patients, already destined to have a poor prognosis, but in whom diagnosis was relatively easy (the so-called 'sick-quick'). Many of these patients will have suffered an emergency complication of their cancer, which brings extra mortality as well as being associated with worse cancer staging [3].

If the 'sick-quick' patients are removed from consideration, then survival worsens with diagnostic delay almost linearly. In a sophisticated modelling exercise Sud et al. estimated survival disadvantage caused by the COVID-19 pandemic for most cancers [4]. Survival for colorectal cancer was worsened by a 2-month delay in a range of 6.4–10.7%, with the smaller reductions being in younger ages. In broad terms this equates to a survival disadvantage of around 1% per week of delay. These figures have to be compared with the benefits accruing

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from adjuvant treatment. It may be that all the survival benefits from adjuvant treatment are of the same magnitude as the survival losses from one month of delay in diagnosis after symptoms have begun.

More evidence for survival gains from expedited diagnosis comes from screening studies [ref Screening paper in this series]. The introduction of bowel screening in the UK was associated with significant reductions in emergency admissions [5]. However, currently the UK national screening programme – which is well organised, and free for users – identifies fewer than 10% of all UK colorectal cancers [6]. Symptomatic detection remains the main route to diagnosis in the UK.

One final point on the survival benefits which arise from expedited symptomatic diagnosis. Some colorectal cancers that are identified in patients investigated for bowel symptoms were not the cause of the symptoms and were found by chance. Not surprisingly these cases are more likely to be found at an early disease stage and have a better prognosis. The percentage of serendipitously found colorectal cancers has been estimated to be between 12 and 32% [7]. There is a positive relationship between the use of suspected cancer investigations in primary care at a practice level, and cancer survival. This advantage has been shown for all cancers collectively [8] and for oesophagogastric cancer specifically [9] though has yet to be examined for colorectal cancer specifically.

In summary, there is mounting evidence for survival benefits from expedited diagnosis of symptomatic colorectal cancer. Indeed, this may be the cancer site with the strongest evidence for the benefits of earlier detection.

## 3. The challenge for primary care

Given that screening picks up such a small minority of cases even in countries with comprehensive screening programmes, most strategies aimed at improving the diagnostic pathway for CRC target the symptomatic patient population. These strategies have two components: identifying who should be investigated for possible colorectal cancer, and how should they be tested. We concentrate on the first of these – selection of patients for testing – as faecal immunochemical testing (FIT) has greatly simplified testing in UK primary care [10]. Before FIT was available, and in countries where it is yet to be introduced, patients who had been identified as having possible colorectal cancer could only be offered colonoscopy, CT, or CT colonography, with a small number being offered capsule endoscopy, though the last of these has yet to be rigorously evaluated in the symptomatic population. Each of these tests is moderately expensive and requires colon preparation. Complications can occur, plus CT delivers a radiation load. Therefore, in most developed countries definitive investigation by one of these testing modalities has been targeted at those most likely to have cancer – that is the higher-risk population. This principle of preferentially investigating the highest-risk patients used in the National Institute for Health and Clinical Excellence Guidelines in the UK, initially in their 2005 document, Referral Guidelines for Suspected Cancer. An explicit threshold of a risk of cancer of 3% or higher warranting urgent investigation was the basis for revised guidance from NICE, published in 2015 [11].

NICE guidance pertains to England and Wales, and is generally followed in Northern Ireland. Scotland has its own guidance, which does not explicitly report a threshold cancer risk for referral. Since publication of NG12 in 2015, the focus within cancer diagnostic research has moved away somewhat from cancer-site centered studies to studies of non-specific features. This term is used to mean features that may represent cancer, but without a specific tie to one particular site or type. Thus, there are recent studies of weight loss [12], abdominal pain [13], thrombocytosis [14] and microcytosis [15] – all with some relevance to colorectal cancer.

## 4. Features of colorectal cancer

The alarm features of colorectal cancer include rectal bleeding, anemia, change in bowel habit, and weight loss; evidence for the clinical value of these features was explored in a recent systematic review [16]. There is an association between some symptoms of colorectal cancer and the cancer stage at diagnosis [17], with rectal bleeding, change in bowel habit, abdominal pain and weight loss increasingly more likely to represent more advanced stage. However, any of the features of colorectal cancer can be found at any stage. In particular, there is no symptom (or pattern of symptoms) which is characteristic of early-stage disease. Therefore, we present symptoms throughout this paper in approximate order of risk. These are summarized in Table 1.

**Table 1**
The major symptoms of colorectal cancer in primary care.

| Feature of colorectal cancer | Approximate risk of colorectal cancer (PPV) | Approximate frequency in primary care series [18] | Notes |
|---|---|---|---|
| Anaemia | In meta-analysis 5.9% | 27% | PPVs higher with iron deficiency and with severity [19] |
| Rectal/ abdominal masses | unknown | Unknown, but likely to be very low | |
| Rectal bleeding | In meta-analysis 4.8% | 42% | PPVs higher with recurrent bleeding [20] |
| Weight loss | <1% in meta-analysis of a systematic review [21] | 27% | The PPV increases with increasing weight loss [22] |
| Abdominal pain | In meta-analysis, 1.0% [11] | 42% | 0.32% in a large recent study [13] |
| Diarrhoea | 0.9% [18] | 38% | See discussion of these three terms in text |
| Constipation | 1 [18]. | 26% | |
| Change in bowel habit | 3.9–14% [22,23] | 20% [23] | |
| Thrombocytosis | 2.3% in males; 1.2% in females [14] | unreported | |

### 4.1. Anaemia

Anaemia arises in colorectal cancer because of bleeding into the colon. This may be invisible, or not be noticed by the patient. This gastrointestinal bleeding is the rationale for faecal immunochemical testing and its predecessor, guaiac testing. The bleeding may also explain the increased platelet count (thrombocytosis) described in more detail below. Prolonged bleeding may deplete iron stores, which are easily measurable – most usually as a ferritin estimation. The red cell volume may also fall, causing microcytosis. Indeed, microcytosis without anemia still represents a small risk of colorectal cancer [15]. As would be expected the risk of colorectal cancer increases as the value of haemoglobin falls, and with increasing patient age [19].

Anaemia may present with symptoms of fatigue or dyspnea, but most commonly is identified as part of a full blood count having been undertaken without colorectal cancer necessarily being suspected. Even so, the mere decision to perform a full blood count selects a population at higher risk of cancer (an approximate doubling of risk). Counter-intuitively, even if the haemoglobin is normal, such patients remain at a higher risk than the population norm [24]. This is simply because the reassurance derived from the normal haemoglobin is smaller than the selection effect in the initial decision to test.

A similar counter-intuitive effect is seen with worse survival outcomes in those with mild anaemia as their first symptom when compared to more severe anaemia [25]. Indeed, those with mild anaemia are more likely to present with an emergency complication of their cancer than their severe anaemia counterparts [26]. This is probably a further manifestation of the 'sick-quick' waiting time paradox,

whereby patients with severe anaemia are referred for investigation without delay, yet those with milder anaemia are investigated more slowly (or not at all).

The assumption that anaemia from colorectal cancer develops slowly and has accompanying features such as microcytosis underpinned a study from Israel, where routine annual full blood counts are offered to the adult population [27]. This routine testing eliminates the selection bias referred to above. However, the performance characteristics of the algorithm were insufficient to support clinical adoption. Several groups are currently examining whether study of primary care blood results with artificial intelligence techniques can produce a useful algorithm.

Investigation of anaemia must consider other possibilities, including benign colonic conditions, upper gastrointestinal lesions – both benign or malignant – nutritional deficiency and drug side-effects, plus several other conditions. Indeed, many other cancers may cause anaemia, so there is interest in investigation for cell-free DNA, in the so called multi-cancer detection test. Secondary care studies have reported good diagnostic performance for such tests, which not only identify methylated DNA as a marker of probable cancer, but can suggest possible cancer sites. Major studies of these multi-cancer detection tests are underway, including in the symptomatic population. As yet, the evidence base is insufficient to support their use in patients with possible colorectal cancer, though this may change.

### 4.2. Rectal/abdominal masses

These are rare but high-risk presentation of colorectal cancer. There is no high-quality evidence from primary care on these features, reflecting their rarity, and perhaps the obvious clinical action to be taken if such a mass is encountered. Nonetheless, it is clear that not all masses that are identified are malignant – though they still warrant investigation.

### 4.3. Rectal bleeding

Rectal bleeding is the commonest presentation of colorectal cancer. For this reason, many different pathways have been used to facilitate rapid investigation of this feature. To an extent this strategy has worked – in England it is the symptom with the shortest time to diagnosis, which may explain the better survival for colorectal cancer patients who present with this symptom when compared to other features of the disease [25,28]. These pathways may now be redundant in the FIT era. It appears counter-intuitive to request a FIT in a patient who describes rectal bleeding: however, the performance characteristics of FIT in primary care are similar whether the population includes or excludes patients with this symptom. The use of FIT in this population also sidesteps the problem of whether to investigate the whole bowel (but colonoscopy or CT colonography) or whether to examine the left side of the bowel (by sigmoidoscopy) as rectal bleeding can occasionally arise from the right side of the bowel.

Studies have examined specific characteristics of rectal bleeding or accompanying symptoms [18,29]. These reported that the presence of perianal symptoms – such as itching – identified a lower risk population with rectal bleeding. The assumption was that haemorrhoids or anal fissures were a more likely explanation and that investigation for possible colorectal cancer could be delayed or even averted. Later studies did not support this view, and given the relative simplicity and inexpensiveness of FIT, it is now deemed appropriate to perform this test irrespective of accompanying features.

### 4.4. Weight loss

This symptom in isolation carries a lower risk for colorectal cancer than those discussed earlier in this section. However, the incidence of any cancer type following unexplained weight loss in primary care is 2.2%, from a recent large study of electronic primary care records [12]. It is likely that there are other symptoms accompanying the loss of weight when it is caused by colorectal cancer, but it is still logical to request a FIT in most patients with unexpected weight loss. Like anaemia, this symptom is a candidate for multi-cancer detection tests, so investigation may switch from FIT and imaging to such tests if they are shown to be useful in current studies. The amount of weight loss required to trigger investigation is unknown, though a loss of greater than 10% of the patient's 'normal' weight has a PPV of roughly twice that for weight loss of 5–10%, across all ages and both sexes [22]. It is often difficult to assess the 'normal' weight, particularly as recording of weight in primary care is infrequent.

### 4.5. Abdominal pain

Several studies have reported an association between abdominal pain and a future diagnosis of colorectal cancer, albeit with low positive predictive values (PPVs) for all cancer types studied. The systematic review undertaken as part of the development of NICE Guidance NG12 [11] identified eight studies, five of which entered meta-analysis. The summary PPV was 2.04% (95% confidence intervals 0.53–7.55) though one study was a clear outlier. Following removal of this study, the summary PPV was 1.02 (0.36–2.69). One large study published after the NICE review reported an even lower PPV of 0.32% [13]. This reflects the large number of benign conditions, and non-colorectal cancers, which can cause abdominal pain. However, that brings the risk of misdiagnosis, including of irritable bowel syndrome. Unfortunately, most of the studies were based on retrospective examination of medical records, so further characterization of the abdominal pain was inconsistent or missing.

Despite its relatively low PPV, abdominal pain cannot be ignored as a symptom of possible cancer. Like mild anaemia, it is particularly associated with poorer outcomes (and with emergency presentations) [25]. Indeed, this may be because of its low PPV, encouraging clinicians to consider other possible diagnoses instead of cancer. This was particularly relevant in the pre-FIT era, where investigation to rule out cancer necessitated colonoscopy or sigmoidoscopy, preceded by administration of bowel preparation. Fortunately, the performance of FIT has eased the problem of whether (and how) to investigate low-risk colorectal cancer symptoms in primary care.

### 4.6. Constipation, diarrhoea and change in bowel habit

Clearly these terms overlap, but change in bowel habit is more than just an umbrella term covering both constipation and diarrhoea. It is a term used only by the medical profession (in forty years of clinical practice, WH never had a patient who used that expression). It means more than just constipation or diarrhoea or both. It has an unspoken extra meaning: 'constipation or diarrhoea, and I think colorectal cancer is possible'. This last clause is crucial, even if unspoken. Medicolegally, if a UK general practitioner documented change in bowel habit in the patient's records and chose not to investigate, they would be deemed negligent. This would not necessarily be the case for records of constipation or diarrhoea. This terminological difference is reflected in very different PPVs, as seen in Table 1. PPVs for change in bowel habit are generally four or times higher than for diarrhoea or constipation. In effect this difference reflects the doctor's holistic assessment – which may be of other symptoms, or may be a subtle intuition that the constipation or diarrhoea is of greater concern. General practitioners' ability to select sub-populations at higher (and lower) risk has been studied in a report of high-risk symptoms of cancer [30]. In over 13,000 patients having rectal bleeding in their records, only 17.7% received a referral for possible colorectal cancer, despite national guidance recommending it. However, the percentage of patients who were referred who transpired to have cancer was 6.4%, and only 1.5% in those un-referred (but who later must have been investigated). In short, general practitioners have the skills to identify higher risk patients – and

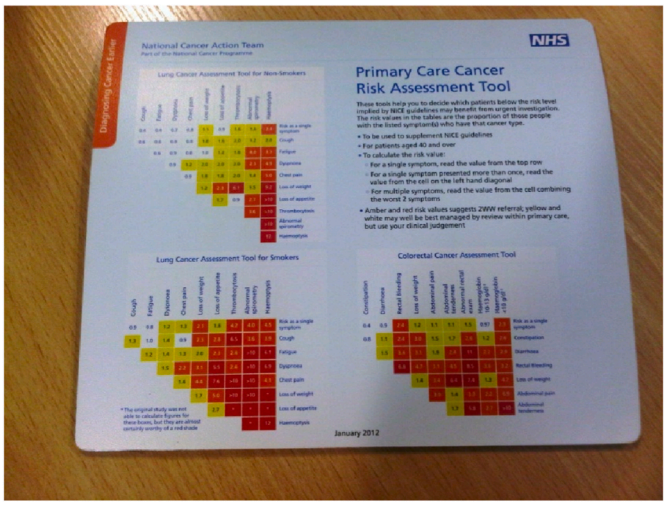


**Fig. 1.** A lung and colorectal Risk assessment tool in mouse mat form.

with disorders of bowel transit, to label them change in bowel habit.

### 4.7. Thrombocytosis

Thrombocytosis is a platelet count above a normal range, though this normal range varies between laboratories and the sexes. Two large studies have examined the association between thrombocytosis and colorectal cancer. Both were large and retrospective, and utilized existing medical and laboratory records plus cancer registries. The first from the UK, used a threshold range of 400 $\times$ $10^9$/litre to define abnormality, and identified a PPV for colorectal cancer of 2.3% in males and 1.2% in females (likely due to the fact that average female platelet counts are higher, with mildly abnormal counts more frequent, thus 'diluting' the cases) [14]. Similar results were reported from a Canadian study, which found a PPV of 1.2% using a threshold of 450 $\times$ $10^9$/litre to define abnormality [31]. These figures are high enough to suggest a FIT should be offered when thrombocytosis is identified. It is also possible that the platelet count can be used in anaemic patients to help identify a higher risk sub-population warring urgent investigation. This is currently being studied.

## 5. Tools to assist the general practitioner

It is clear from the above that colorectal cancer can present in several ways: indeed the described features of colorectal cancer are often found together (and represent higher PPVs when they do). However, many of the symptoms are extremely common in the non-cancer population. Therefore, it is not surprising that doctors may simply not consider the possibility of cancer in many of these presentations, resulting in increased time to diagnosis. A second broad reason for diagnostic delay occurs when cancer is considered, but there are barriers to investigation.

The first of these problems can be addressed by providing cancer diagnostic information to general practitioners in a way that reduces the chance that cancer will not be considered. This information can be delivered in several ways. To illustrate these, we reference Risk Assessment Tools, a group of 18 adult charts (one for each common adult cancer) showing the risk of cancer for symptoms expressed as a PPV. Other tools exist, including QCancer, which covers fewer cancer sites, and is only available in electronic form. Initially, Risk Assessment Tools (or RATs) were given to all English general practitioners in mousemat and calendar forms, and covered only colorectal and lung cancer (see Fig. 1).

Each cell in the top row reports the risk of colorectal cancer for a single symptom, colour-coded to reflect the risk. Cells on the intersect of two symptoms reported the risk when both symptoms were present

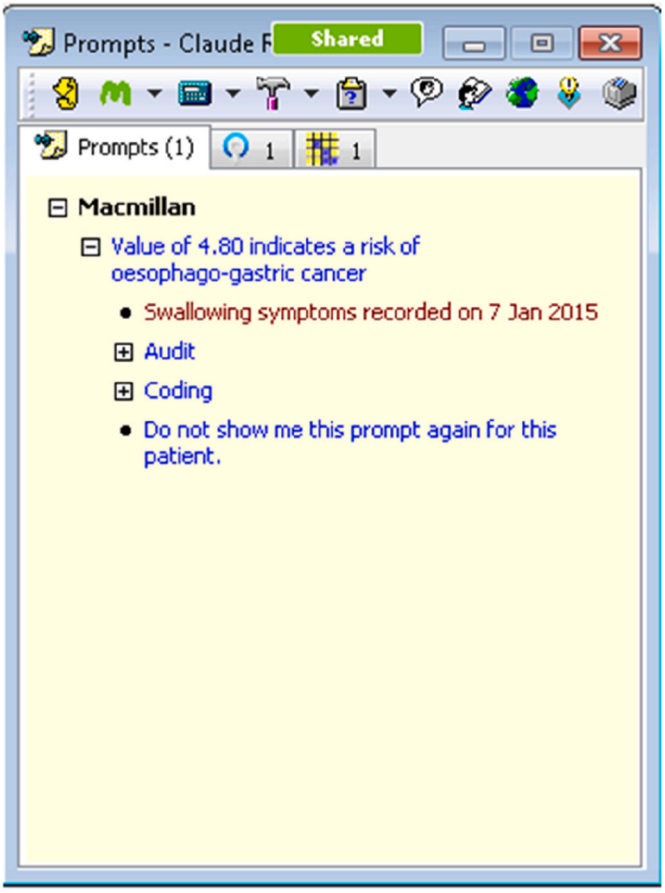


**Fig. 2.** A sample prompt from an eRAT, based on a fictitious patient.

(strictly, when they had been reported within the same 24 month period, though they were usually very close together). Finally cells on the diagonal reported the risk when a symptom had been reported at least twice (again within a 24 month period).

The next phase in development was to integrate RATs into general practitioners' computers, so that they would automatically search the patient's medical record for reports of any of the symptoms, and then calculate the risk of cancer represented by this symptom or symptoms. These were named eRATs to differentiate them from the paper/mouse mat forms earlier. If the risk was above an agreed level a prompt would show on the GP's computer screen (see Fig. 2). We chose a 2% risk as a balance between aspiring to diagnose cancer earlier vs. avoiding generating so many prompts that the GP may end up ignoring many. This so-called 'prompt fatigue' is a genuine phenomenon.

The early work in eRATs was supported by a UK Cancer charity, Macmillan, who distributed them to interested general practitioners. By 2015, cancer decision support tools were available in just over a third of English practices, though only half of such practices actually reporting using them [32].

A large cluster-randomized trial is currently under way to examine the clinical and cost-effectiveness of eRATs (the ERICA trial) [33]. In over 400 practices, eRATs for six adult cancers (including colorectal) have been installed in the intervention practices. The primary outcome of the trial is stage at diagnosis, as this is so clearly linked with survival. Multiple secondary outcomes are being examined, as well as a process evaluation and economic arms. Practice recruitment ceased in April 2022, and the trial runs for 24 months. The cancer outcome data is to be extracted from routine cancer registry records, so that the final result should be available in late 2025.

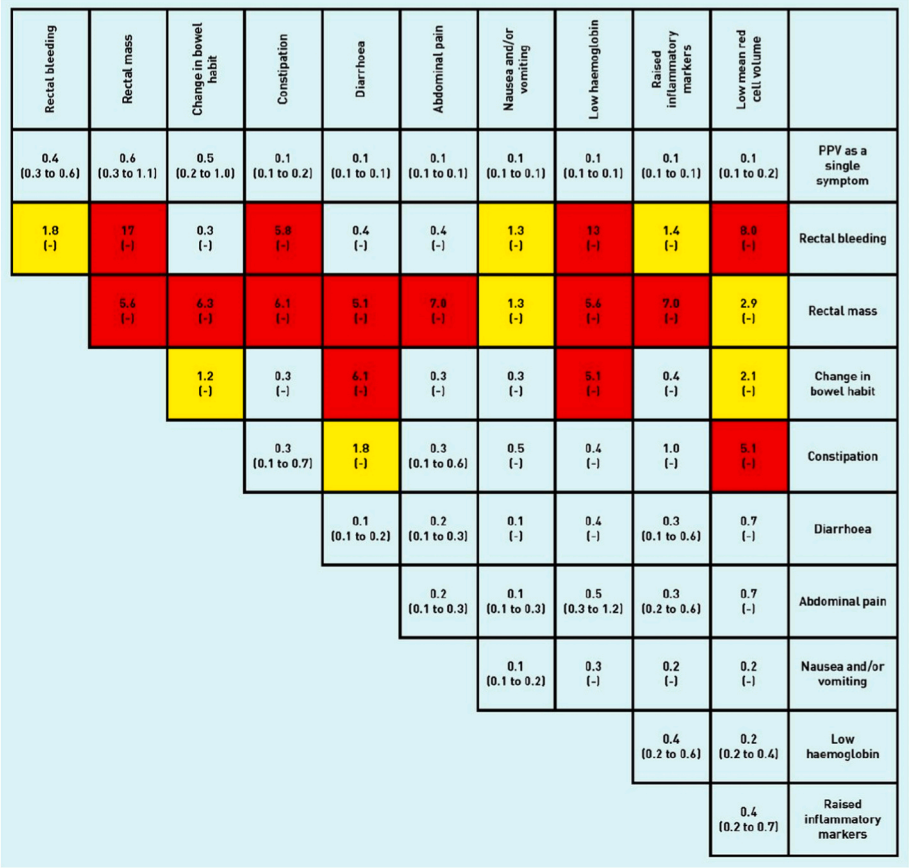


**Fig. 3.** PPVs (95% CI) for colorectal cancer (CRC) in males and females aged 18–49 years for individual risk markers and for pairs of risk markers in combination. PPV = positive predictive value. (reproduced with permission from Stapley et al.).

## 6. Education and guidance

The clinical decision support in the form of RATs and QCancer are also educational. However, the most influential form of education/guidance in the UK has been NICE guidance, most notably NG12, Suspected Cancer: recognition and referral [11]. This was published in 2015, and replaced guidance for 2005. The colorectal guidance was controversial in recommending testing for blood in faeces, a test strategy that had been abandoned many years before, because of the level of false-negatives. Awkwardly, at the time of NICE's systematic reviews there was very little primary care evidence on the use of FIT in the symptomatic population, whereas there was supportive evidence for the older guaiac test, or faecal occult blood test (FOB). Thus the 2015 recommendation for testing for 'occult blood in faeces' had to be later replaced by a recommendation for FIT in a second NICE guidance, DG30 [34].

Despite the controversy, this colorectal guidance has resulted in reduced times to diagnosis. A study examined the time to diagnosis for colorectal cancer symptoms newly introduced in 2015 ('new symptoms'), and compared them to times to diagnosis for symptoms that were present in both the previous 2005 guidance and the 2015 guidance ('old symptoms') [35]. Before the 2015 guidance was issued, not surprisingly, patients with old symptoms had their colorectal cancer diagnosed more rapidly than patients with new symptoms (which were of course not in the guidance at all). After 2015, patients with new symptoms had more rapid diagnoses, initially matching those of patients with old symptoms, and eventually doing better, so that at the end of the study patients with new symptoms were receiving a faster diagnosis than those with 'old' traditional symptoms.

However, education and guidance is only as good as the research upon which it is based. Some problem areas in colorectal diagnostic research remain. In particular, characteristics of symptoms such as duration and severity have very little research support. Proxies such as re-attendance with the symptom are of some value, but it is simply unknown what the risk of colorectal cancer is for say 2 weeks of diarrhoea as opposed to six weeks of diarrhoea. Clinical experience suggests the longer duration is likely to represent a higher risk, but is the risk increase linear? And for how long does the risk rise? It seems to rise with each primary care presentation with abdominal pain (at least up to the sixth presentation [18]) but beyond that is unknown, and it is likely other diseases such as irritable bowel syndrome, become much more likely if the symptom has persisted over a year. Research in this area is difficult, but there is an unmet need for it.

## 7. Younger patients

Colorectal cancer in the under 50-year-old age group is increasingly common; the incidence in this age group has almost doubled in the last 30 years [36]. Some reasons for this are given in an earlier paper in this issue [ref], with lifestyle factors being more relevant than inheritable predisposition, in that around a fifth only of cancers in this age group are found to have a recognized genetic predisposition [37]. The symptoms in younger patients are no different to those in older patients (Fig. 3) [38].

However, because of the relative rarity of colorectal cancer, each specific symptom (or pair of symptoms) has a lower PPV – often much lower -than in studies including all ages. This creates a problem for primary care in that a general practitioner is less likely to consider cancer than they would have been for the same symptom in an older patient. Furthermore, most inflammatory bowel disease is first

experienced below the age of 50. These diseases share some symptoms, so that in this age group it is more likely that a patient reporting one or more of these symptoms has inflammatory bowel disease than cancer. The main primary care test for inflammatory bowel disease, calprotectin, does not reliably also identify cancer, so if such patients are investigated with calprotectin alone, cancer may not be identified. FIT may help, but again both diseases exhibit rectal bleeding [39]. All these factors mean that diagnosis may be delayed: indeed the stage distribution and thus long-term survival have been reported to be worse in younger patients than older patients [40].

There is no simple solution to diagnosis of colorectal cancer in younger patients. Increased use of FIT, and of calprotectin, should identify patients in whom definitive bowel investigation by colonoscopy is warranted. However, that requires the clinician to have thought of cancer (or inflammatory bowel disease) in the first place. It is plausible electronic prompts could help here, though this is as yet unknown.

## 8. Factors affecting risk

### 8.1. Genetic risk

Lynch Syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited genetic disorder that predisposes affected individuals to several cancer types, including colorectal, endometrial, ovarian, gastric, and pancreatic. Lynch syndrome is associated with a much higher lifetime risk of developing colorectal cancer than the general population; estimated to be between 52 and 82% [41], compared to 5–6% in the general population. The risk of early onset (before age 50 years) colorectal cancer is much higher in Lynch Syndrome [42].

There is no routine testing for Lynch Syndrome in the UK; rather, targeted screening is recommended for individuals with a personal or family history of colorectal or other Lynch syndrome-associated cancers [7]. Thus, identification of patients occurs after the suspicion, or confirmation, of cancer has been raised, making this knowledge of limited use in the investigation of symptomatic patients in primary care. Regular screening for colorectal cancer in individuals identified with Lynch includes colonoscopies every one to two years from 25 years of age [43]. Five-year survival from colorectal cancer diagnosis in patients with Lynch was found to be 90% in a meta-analysis [44]; it is only around 50% in all cases in the UK [45], perhaps reflecting the impact of regular colonoscopy screening in the former group.

Genetic risk scores (GRS) have recently attracted interest as a potential tool to identify individuals at risk of cancer, who could then be monitored, or investigated in primary care when they present with nonspecific signs of disease [46]. Research on the impact of GRS in the symptomatic pathway is limited to prostate cancer so far [47], but research into the potential use of a colorectal cancer GRS is ongoing.

### 8.2. Chronic health conditions

Several chronic health conditions are known to have an effect on colorectal cancer risk; however, little is known about the impact these conditions may have on symptomatic presentation. Diabetics have an increased risk of developing colorectal cancer compared to non-diabetic patients (relative risk 1.28; 95% CI 1.19–1.39) [48]; this increase may be due to several factors, including insulin resistance, chronic inflammation, and hyperglycemia, which are all characteristics of diabetes and have been linked to cancer development [49]. Hypertension [50], obesity [51], inflammatory bowel disease [52] are also known to increase colorectal cancer risk, although the mechanisms underpinning these links is not fully understood. Despite this, current guidance for primary care in investigating symptomatic patients does not offer alternative options depending on the presence (or absence) of comorbidities [11].

## 9. Testing strategies

Access to diagnostic tests is an important factor in improving the diagnostic pathway for colorectal cancer. The issues surrounding access to tests varies depending on the healthcare system; in the UK, some tests are available for general practitioners in primary care, with others requiring referral to secondary care. Waiting times for investigations such as colonoscopies can be lengthy in the UK (although this is less of a concern in other countries), a problem compounded by the COVID-19 pandemic, from which the service is still recovering. This can delay diagnosis and treatment, which can impact patient outcomes.

One approach to improving access to diagnostic tests in primary care is to increase the use of non-invasive diagnostic tests. Faecal immunochemical tests (FIT) test for the presence of haemoglobin in a faecal sample. They can be ordered directly in primary care and completed by the patient at home, which can help to reduce the burden on healthcare systems and improve access for patients. FIT is in widespread use in the UK, with variable use in other countries.

Faecal DNA tests are an emerging point-of-care test which detect specific genetic alterations and epigenetic changes associated with colorectal cancer in faecal samples. The detection of these biomarkers can indicate the presence of colorectal cancer or its precursor lesions. Faecal DNA tests have not been evaluated extensively in the primary care setting; a systematic review published in 2020 concluded that these tests may be useful for colorectal cancer detection, but that candidate tests need to be evaluated in large longitudinal studies in both symptomatic and asymptomatic populations [53]. Long-term studies assessing the impact of faecal DNA testing on colorectal cancer incidence and mortality are underway to establish its role in population-based screening programs and in symptomatic detection.

Capsule colon endoscopy (CCE) uses advanced imaging technology to create a detailed image of the colon, which can help to identify abnormalities and lesions. It offers an alternative to the traditional colonoscopy and has the advantage of being less invasive than that traditional method, eliminating the need for sedation. The patient swallows the capsule, containing a camera and a light, which captures footage of the bowel as it moves through the patient. The footage is collected by an external recording device. CCE is currently available in secondary care and is a potential addition to the primary care pathway. CCE has been demonstrated to be more tolerable to patients than the traditional colonoscopy [54]. This can lead to improved compliance and increased participation rates in testing. The method enables the entire colon to be imaged, including regions which may be challenging to reach with a traditional colonoscopy. However, finding and training staff in interpreting the outputs remains a challenge, and the diagnostic accuracy in the primary care population is unknown. CCE cannot biopsy any suspicious region or perform therapeutic tissue removal, so a follow up with a traditional colonoscopy is still required in patients who test positive, either for biopsy or for polyp removal. There are also issues with incomplete imaging of the bowel, image quality, and in some cases capsule retention. Factors such as bowel motility, bowel preparation quality, and anatomical variations can impact the procedure's effectiveness.

In addition to these approaches, there is also a need to improve the coordination and communication between healthcare providers in the diagnostic pathway. This can help to ensure that patients receive timely and appropriate care, and that the diagnostic process is as efficient as possible.

## 10. Patient awareness

Improving symptomatic colorectal cancer detection in primary care settings relies on patients finding their way to primary care with their symptoms. A number of public health campaigns have attempted to increase awareness of the important features to look out for. These include Be Clear on Cancer, a national public awareness campaign that

## Research agenda

- Further clarification of symptom characteristics, such as duration and severity
- Whether the risks of symptoms are changed when the patient has a hereditary syndrome, or other genetic predisposition to colorectal cancer
- Whether the risk of colorectal cancer associated with selected bowel symptoms is different in patients with common comorbidities

## Practice points

- Identification of symptomatic colorectal cancer rapidly yields survival benefits
- The features of colorectal cancer are well known, and the same in older and younger patients, though individually represent a lower risk of colorectal cancer in the young
- The faecal immunochemical test (FIT) is now available for patients with symptoms of colorectal cancer, and is widely available in some countries in Europe including UK primary care
- Patients with comorbidities, such as diabetes or obesity, may experience a longer time to diagnosis compared to patients without comorbidities.

aimed to improve early diagnosis of several cancer types by raising awareness of symptoms and encouraging people to see their doctor earlier. The campaign included specific messages about bowel cancer, such as "If you've had blood in your poo or looser poo for the last three weeks, tell your doctor". "Never Too Young", from Bowel Cancer UK, aimed to raise awareness of bowel cancer in younger people. Cancer Research UK carries out numerous public information campaigns, as does the UK National Bowel Screening Programme. Research evidence on the effectiveness of these programmes is limited. An evaluation of Be Clear on Cancer found increases in colorectal cancer were mostly in the 'worried well', and increased the demand on NHS resources without any discernible improvements in cancer outcomes [55].

### 11. Conclusion

Improving the symptomatic colorectal cancer detection pathway is crucial for improving early diagnosis and patient outcomes. A range of strategies are required to achieve this improvement; this must be underpinned by high quality health research. Innovative approaches that prioritize the identification of patients who are at higher risk of developing the disease are needed, as well the development and implementation of more efficient and accessible diagnostic tools. By implementing innovative approaches, optimizing diagnostic tools, and improving patient education and awareness, we can improve the overall quality of care for patients with colorectal cancer.

### Declaration of competing interest

William Hamilton and Sarah Bailey have each received multiple research grants from governmental, charity and philanthropic sources to research aspects of cancer diagnosis. William Hamilton owns intellectual property in Risk Assessment Tools, but has no plans to commercialize this.

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