



Recognising Colorectal Cancer in Primary Care

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ABSTRACT

Colorectal cancer (CRC) is the third most common cancer worldwide. Primary care professionals can play an important role in both prevention and early detection of CRC. Most CRCs are attributed to modifiable lifestyle factors, which can be addressed within primary care, and promotion of population-based screening programmes can aid early cancer detection in asymptomatic patients. Primary care professionals have a vital role in clinically assessing patients presenting with symptoms that may indicate cancer, as most patients with CRC first present with symptoms. These

assessments are often challenging—many of the symptoms of CRC are non-specific and commonly occur in patients presenting with non-malignant disease. The range of options for investigating symptomatic patients in primary care is rapidly growing. Simple tests, such as faecal immunochemical testing (FIT), are now being used to guide decisions around referral for more invasive tests, such as colonoscopy, while direct access to specialist investigations is also becoming more common. Clinical decision support tools (CDSTs) which calculate cancer risk based on symptomatology, patient characteristics and test results can provide an additional resource to guide decisions on further investigation. This article explores the challenges of CRC prevention and detection from the primary care perspective, discusses current evidence-based approaches for CRC detection used in primary care (with examples from UK guidelines), and highlights emerging research which may likely alter practice in the future.

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Key Summary Points

Colorectal cancer (CRC) is the third most common cancer worldwide; primary care has a key role in its prevention and early detection.

Symptom assessment in primary care is challenging as CRC symptoms are often common and non-specific, but there are several options to guide decisions around referrals and examinations.

This article provides a practical resource for primary care professionals, describing current evidence-based approaches and emerging research for the early detection of CRC, including the increasing role of the faecal immunochemical test (FIT) for triaging symptomatic patients in primary care.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to <https://doi.org/10.6084/m9.figshare.14270441>.

INTRODUCTION

Colorectal cancer (CRC), comprising cancers of the colon and rectum, is the third most common cancer type and the second most common cause of cancer death worldwide, with over 800,000 deaths globally in 2018 [1–3]. Most CRCs develop from adenomatous polyps or adenomas; the most common subtype of CRC is adenocarcinoma (85% of cases) [4]. CRC diagnosed at later stages is associated with shorter survival time [5]. In England, while 5-year age-standardised survival rates are 91.7%, 84.1% and 64.9% when CRC is diagnosed in stages I, II

and III (respectively), this is reduced to 10.3% when diagnosed with metastases at stage IV [6].

In countries where general practitioners (GPs) play a gatekeeping role, patients usually present first in primary care with symptoms that may indicate cancer. However, many of the gastrointestinal symptoms caused by CRC, such as change in bowel habit, are common, often non-specific, and most people presenting with them will not have cancer [7–9]. This presents a key diagnostic challenge for GPs—how to promptly identify the small number of symptomatic patients with cancer from the large number without? To facilitate this, a number of guidelines, diagnostic tools and strategies have been developed.

This review offers a practical resource for primary care professionals when assessing patients with possible CRC symptoms. First, we discuss the epidemiology of the disease and the role of CRC screening, outlining how primary care may contribute to this. Then, we focus on the clinical assessment of patients in primary care, providing specific UK examples (with relevance to primary care in other countries). Finally, we highlight promising diagnostic developments.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EPIDEMIOLOGY AND RISK FACTORS

Globally (although with substantial heterogeneity), age-standardised incidence rates for CRC have increased in the past 30 years [10]. Increases are occurring in less developed countries in Eastern Europe, Asia and South America, while trends towards stabilisation or decreased rates are noted across highly developed countries such as the UK [3]. Beyond population ageing, rises in incidence can be attributed to changes in lifestyle including alcohol consumption, obesity, smoking, limited physical activity and poor diet (i.e. red and processed meat consumption, insufficient fibre and calcium) [3, 4, 10–12]. Figure 1 describes several

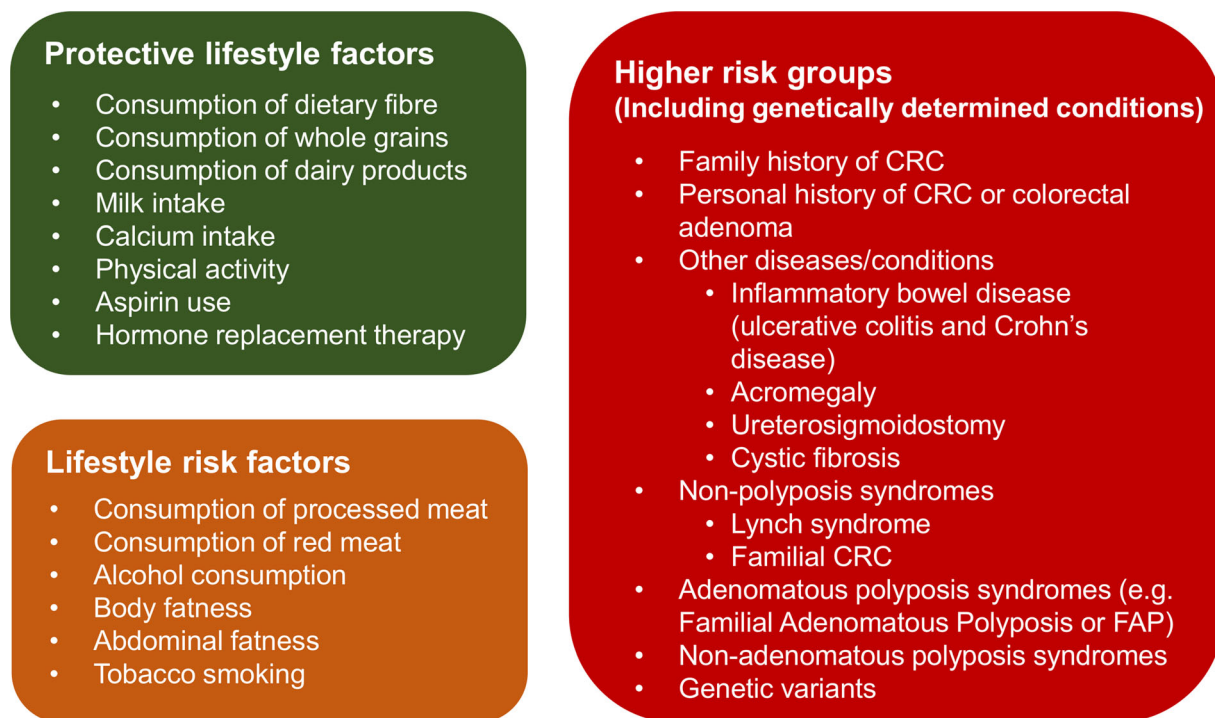


Fig. 1 Protective and risk factors for colorectal cancer. Source: Created with evidence from [4, 14]

lifestyle factors which can protect or increase CRC risk. In the USA, CRC has the second highest number of cancer cases and deaths attributed to lifestyle factors [11]. In the UK, over half of CRC cases can be attributed to lifestyle factors [12]. For primary care, the key implication is that behaviour change interventions, such as those focusing on diet or physical activity, may help to reduce CRC burden [13].

In contrast with incidence rates, age-standardised mortality rates (again with substantial heterogeneity) have decreased worldwide [10]; this has been attributed to the introduction of organised screening programmes and other strategies to promote early cancer diagnosis (e.g. urgent referral pathways; rapid access to diagnostics), and improvements in treatment [3, 4, 10].

Worldwide, CRC is more common in men than women (a 1.47 male-to-female ratio in incidence rates) [4]. CRC risk increases with age, with nine in ten cases diagnosed among people aged 50 years and older [15, 16]. Nevertheless, recent studies in developed countries (including the USA, Canada, Australia and the UK) show

significant increases in incidence rates among those under 50 [17–20]. It is important to be mindful of these changes when assessing younger patients presenting with relevant symptoms in primary care.

Certain populations are at a higher risk of CRC (Fig. 1); these include those with genetic conditions such as Lynch syndrome [4]. Personal history of colorectal adenomas and/or family history of CRC (a two-fold increase in risk if a first-degree relative has CRC) are also known risk factors [4]. Other conditions that increase CRC risk include the main inflammatory bowel diseases (IBDs) ulcerative colitis and Crohn's disease, particularly if conditions are untreated, severe, or are present for a longer time period [4]. Surveillance is often recommended in these cases [21–23].

SCREENING

Organised CRC screening programmes aim to identify cancer in asymptomatic patients (when the disease is more likely to be at early stage)

and has been shown to reduce CRC mortality [24–28]. Screening also facilitates removal of adenomas and other polyps before they become cancerous, helping to prevent CRC [4]. Population-based CRC screening is well established in several countries worldwide (including the UK, USA and Australia), with variation in the screening tests used, time intervals and eligibility criteria [29]. In England and Wales, people aged between 60 and 74 are invited by post to participate in a biannual screening programme; the age threshold is lower in Scotland (50–74 years) [30]. While population-based CRC screening is not usually carried out in primary care, substantial international and UK evidence show that primary care endorsement (such as sending personalised reminder letters or discussing pros and cons of screening with patients) has a key role in improving CRC screening participation [31–37].

The faecal immunochemical test (FIT) was recently introduced in the UK, replacing the guaiac faecal occult blood test (gFOBT) to detect occult blood in asymptomatic individuals [38]. FIT has several advantages over gFOBT, including an increased sensitivity and specificity, better sensitivity to detect advanced adenomas, and only requires a single stool sample. FIT is specific to human haemoglobin, does not require dietary restrictions, and the results are unaffected by the use of non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants [39–42]. Using FIT instead of gFOBT also increases screening participation [40, 43–46]. FIT thresholds/cut-off points for screening vary, even across UK countries (currently 80 µg/g in Scotland, 120 µg/g in England and 150 µg/g in Wales) [47–49]. Those with a result at/above the threshold are referred for a colonoscopy. In addition to FIT, individuals aged 55 in some UK areas are invited to participate in a ‘one-off’ screening sigmoidoscopy, estimated to have led to a 26% reduction of CRC incidence two decades post-intervention [50].

Organised screening identifies a minority of CRCs, with a recent study involving six highly developed countries estimating from 6.3% to 31.4% of all diagnoses [51]. In England, the most recent National Cancer Registration and Analysis Service analysis of routes to diagnosis

show the proportion to be 8% (from 2006 to 2016) [52]. This highlights the need to engage with screening to maximise informed participation, and also shows the vital role of clinically assessing patients presenting with symptoms in primary care for CRC—this is how most patients with the disease present.

SYMPTOMATIC PRESENTATION IN PRIMARY CARE

Most patients diagnosed with CRC will have presented in primary care with one or more abdominal complaints before diagnosis [53, 54]. Lower gastrointestinal symptoms require clinical and family history, physical examination (including abdominal and rectal examination), and routine blood tests (to exclude anaemia and other clinical features) [55]. Symptoms may overlap for cancer and other non-malignant gastrointestinal conditions such as diverticular disease or diverticulitis, IBD, and irritable bowel syndrome (IBS). Figure 2 describes the National Institute for Health and Care Excellence (NICE) guidance (adopted in England, Wales and Northern Ireland) for diagnosing such conditions when cancer is not suspected [56–58]. Safety-netting is required if no causes for the presenting symptoms are identified and they persist over time [59, 60].

CRC has a broad symptom signature (Fig. 3) with varying predictive value [61]. Rectal bleeding is a common presenting symptom although wide variation is reported across studies (16–60%); a large proportion of patients with CRC will not present with this symptom [61, 62]. Other common presenting symptoms are abdominal pain, weight loss, tiredness and changes in bowel habit, particularly looser or more frequent stools [61]. Important clinical features of CRC are iron-deficiency anaemia, abdominal tenderness and abnormal rectal examination [63]. If multiple symptoms/features are present, this increases the likelihood of a patient having CRC but positive predictive values (PPV; the chance of a patient with a symptom/feature combination having cancer) rarely exceed 10% [9, 63].

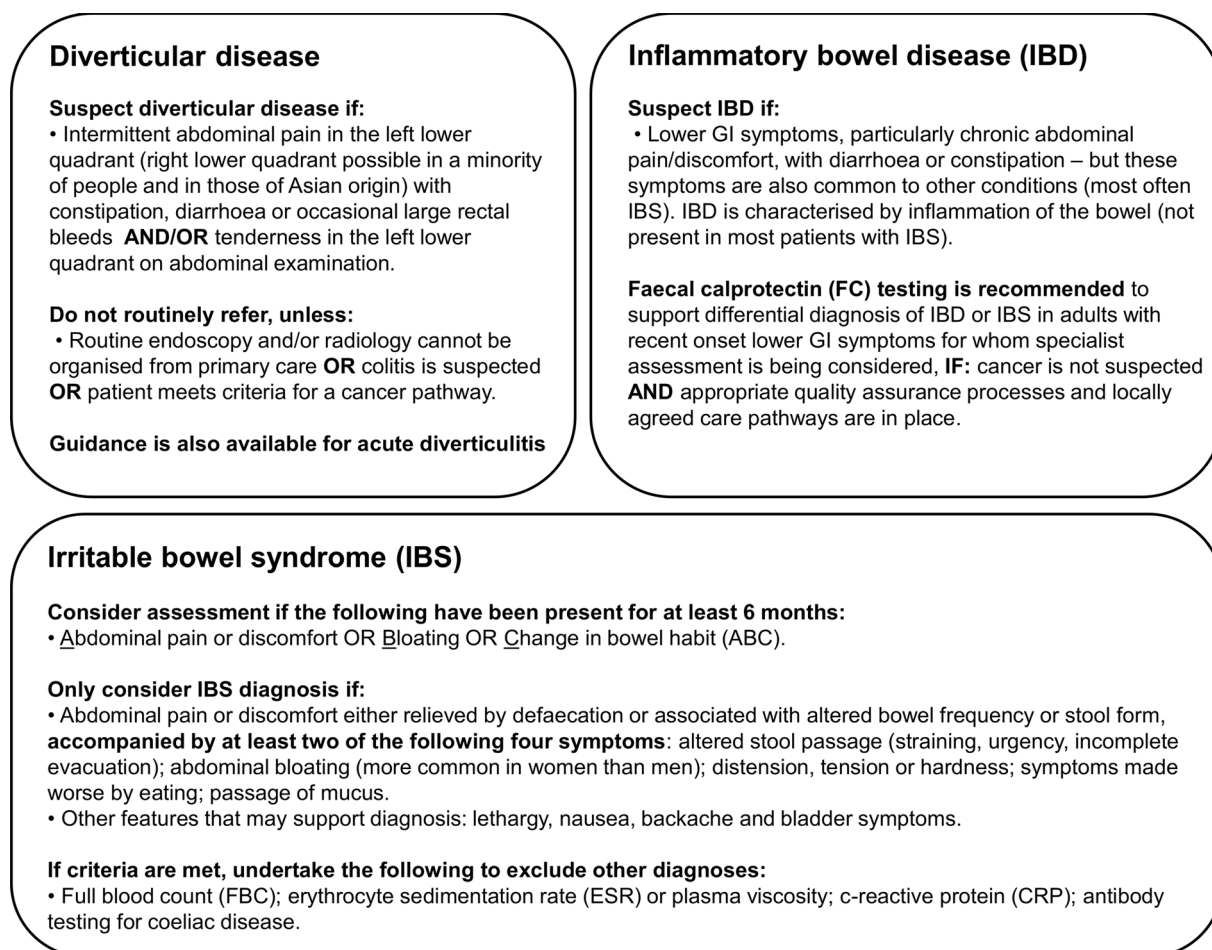


Fig. 2 Common non-malignant bowel conditions and associated NICE guidance. Source: created with evidence from NICE guidance [56–58]

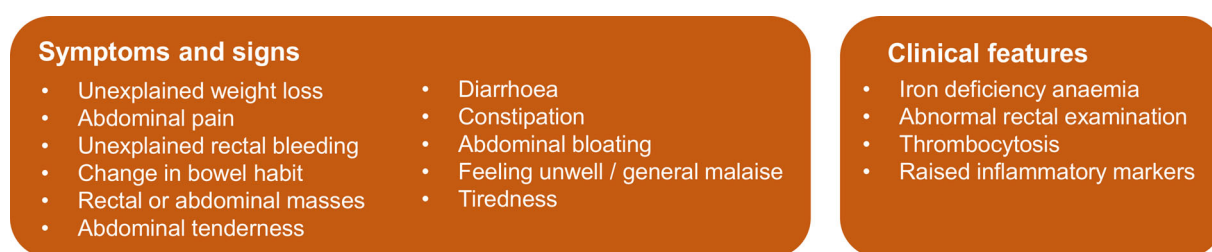


Fig. 3 Symptoms and clinical features that may indicate CRC. Source: created with evidence from [64–66]

There is also emerging evidence that raised platelet count (thrombocytosis) is a risk marker for different types of cancer, including CRC [55, 67]. Raised inflammatory markers (C-reactive protein, erythrocyte sedimentation rate and plasma viscosity) are associated with an

increased risk of cancer, but the sensitivity for these markers is too low to warrant their use to rule out CRC in primary care [68].

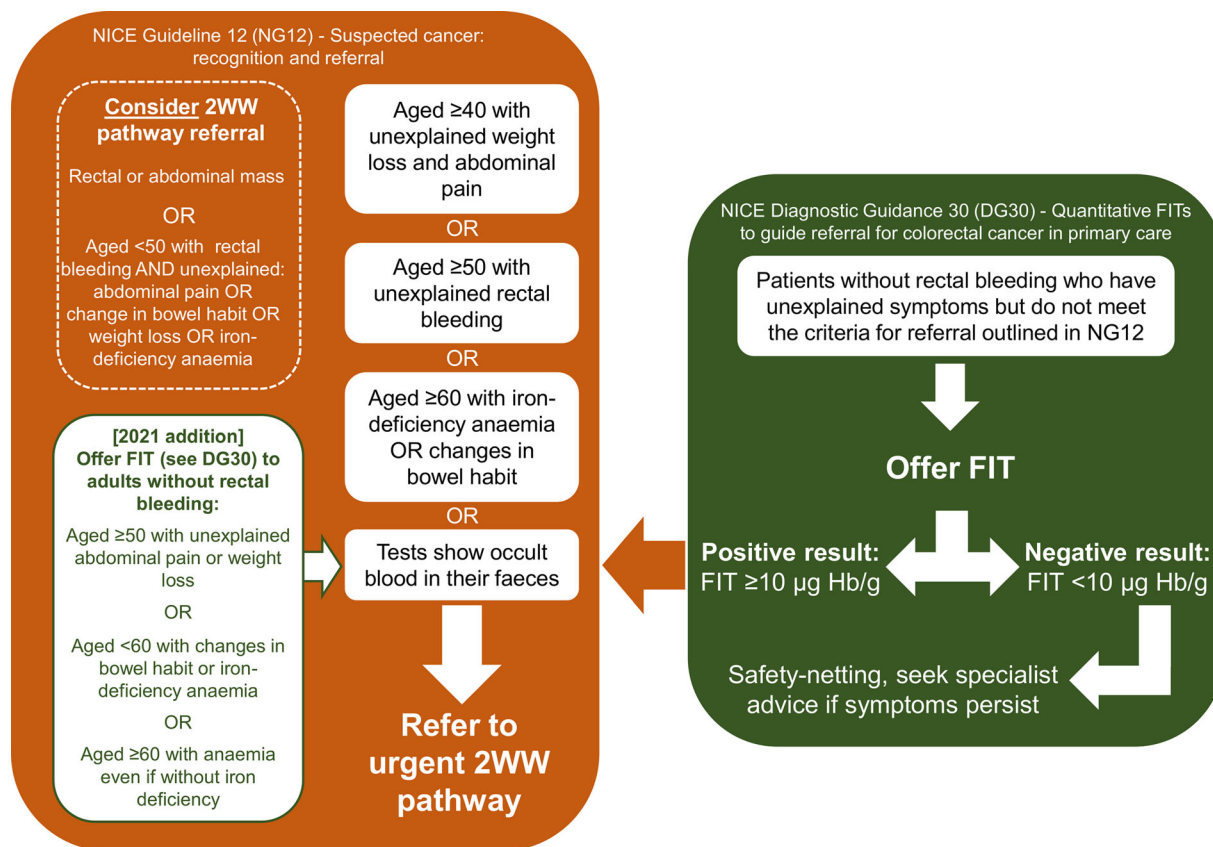


Fig. 4 NICE guidelines when there is a suspicion of CRC. Source: Created with evidence from [38, 65]

REFERRAL AND INVESTIGATIONS

The 2015 NICE guidelines for patients with a suspicion of cancer (known as urgent or 2-week wait referrals) uses age-based symptom cut-offs for patients presenting with alarm or “red flag” symptoms and/or clinical features which have a PPV of 3% or higher (Fig. 4) [65]. This pathway ensures that patients with such features have rapid diagnostic assessments, most often a colonoscopy. Increased use of the urgent referral pathway has shown to be significantly associated with lower CRC mortality, although no associations have yet been found between pathway use and reduction in late-stage cancers [69, 70].

Non-specific symptoms or vague, “low-risk but not no-risk symptoms” that do not meet the urgent referral threshold still carry a risk of cancer [63]; younger patients with such symptoms may also need to be investigated. The

2017 NICE guidelines DG30 [38] (Fig. 4) recommends these patients are offered FIT by GPs, using one of three FIT assays: OC Sensor, HM-JACKarc or FOB Gold [38]. Specifically, FIT should be offered for patients without rectal bleeding who have unexplained symptoms that do not meet criteria for urgent referral. FIT for symptomatic patients uses a threshold of 10 µg Hb/g faeces—much lower than that adopted when FIT is used for screening (recognising the increase in risk for symptomatic patients). Because of the different thresholds, patients meeting criteria should still be offered a FIT even with a recent negative screening result. If the FIT result is positive, the patient can be urgently referred.

A review that informed NICE DG30 reported that at a 10 µg Hb/g level, FIT had sensitivity between 92% and 100% and could rule out CRC in approximately 75–80% of all symptomatic patients. The negative predictive value (which

takes into account disease prevalence) ranged from 99.4% to 100% [71, 72]. When the result is negative the clinician can be confident the patient is very unlikely to have CRC, and provide reassurance. Unnecessary colonoscopies or similar investigations are also avoided. Vigilance is crucial in primary care, both when results are positive and patients are not diagnosed with cancer, and when results are negative. While most patients with a positive FIT result will not have cancer (a recent study showed that 7% of those with a positive FIT had CRC) [73], many will have another significant bowel disease [72]. Since it is still possible (though very unlikely) that a patient with a negative FIT result has cancer, GPs should emphasise the need for patients to seek help if symptoms persist (safety-netting) [59].

Most of the studies that informed the NICE DG30 were carried out in secondary care populations, and only a few countries (including England, Australia and Spain) officially recommend using FIT in primary care to triage patients [74]. Since the guidelines were published, further studies have provided more evidence on FIT's utility in primary care, not only to rule out (most evidence) but also to rule in (least evidence) CRC [59, 73, 75–81]. While a recent survey of 1024 GPs in England found that less than half recognised DG30 [82], it is likely that awareness has increased recently owing to FIT availability, and the increasing use of FIT as a result of limited colonoscopy capacity exacerbated by the COVID-19 pandemic, including to triage patients referred on the urgent pathway [83, 84]. While some guidance has been published on such use [85], evidence on its impact is still limited and it is unclear whether FIT will continue to be used as such (and to what extent) after the COVID-19 pandemic.

DIAGNOSIS

Colonoscopy remains the gold standard investigation for diagnosing colorectal cancer, with histological proof of diagnosis through a biopsy [64]. It is highly sensitive (89–98% for adenomas of at least 10 mm in size, and 75–93% for

adenomas of at least 6 mm in size), [42] and has a relatively low risk of complications, with low perforation (0.08–0.2 per 1000 procedures) and bleeding rates (0.8–2.4 per 1000 procedures) [4]. Alternative investigations are available to deal with limited colonoscopy availability and to meet patient needs when colonoscopy is contraindicated (e.g. frail elderly). These include flexible sigmoidoscopy and the less invasive CT colonography (also called virtual colonoscopy) [64]. While CT colonography is a safe alternative to colonoscopy, it has been found to be less sensitive for smaller polyps [4, 86] (this could be due to perceptual errors that may be improved with training) [87], has a lower detection rate for high-risk serrated lesions [88] and is associated with higher referral rates for additional examinations [89]. Colon capsule endoscopy (patient swallows a camera pill that takes pictures of the bowel as it passes through—these pictures are beamed to a recording device that the patient wears at their waist) is a new alternative. Previously only used in the specialist setting because of its high cost [9, 90], recent limited availability of colonoscopy and patient reluctance to undergo testing in hospital settings because of the COVID-19 pandemic has led to its evaluation as a triage test for moderate to high-risk symptomatic patients [91]. Colon capsule endoscopy is also being trialled in Scotland [92].

RECENT AND FUTURE DEVELOPMENTS

This section describes recent developments with applicability to primary care settings: electronic tools to aid risk assessment and triage, GP direct access to tests, development of rapid diagnostic centres, and use of novel biomarkers. Artificial intelligence may also aid CRC diagnosis in the future, but evidence is still limited [9, 93, 94].

Electronic Tools to Aid Risk Assessment and Triage

Clinical decision support tools (CDSTs) have been developed to allow GPs to make the most

of data available in patient medical records (such as symptoms, patient characteristics such as age and sex and test results) in order to calculate patients' risk of cancer [95–97] (Box 1).

Box 1. Risk Prediction Tools and Models

In the UK, the best known risk prediction tools are the electronic Risk Assessment Tools (eRATs) [63, 98], QCancer© [99–101] and MacMillan Clinical Decision Support tools which combine eRATs and QCancer© [102]. eRATs were derived from case-control studies in primary care and estimate cancer risk for each patient, describing the PPV for single or repeated symptoms [98]. A trial evaluating their clinical and cost effectiveness is under way [103]. QCancer© was derived from a primary care database (QResearch); it estimates cancer risk for symptomatic or asymptomatic individuals, considering not only symptoms but other risk factors such as age, sex, smoking status and family history [99]. Recent evidence indicates that although widely available, such risk prediction tools are still underused in primary care [104]. While they may benefit clinical decision-making, several challenges with implementation have been highlighted [105, 106].

More recent risk prediction models combine patient data and results from biomarker tests. Examples include the CEDAR trial in the Netherlands which combined routine data with results from FIT and faecal calprotectin to rule out significant colorectal diseases [107], and the COLONPREDICT studies in Spain that validated a CRC prediction model based on clinical information and test results (FIT and other biomarkers) and developed a score (FAST) to predict CRC using FIT results, age and sex [108, 109]. The FAST score has recently been evaluated in Scotland; results showed it did not enhance the utility of FIT used alone [110].

Direct Access to Tests and Development of Rapid Diagnostic Centres

Recognising challenges in diagnosing cancers with varied symptomatology, different diagnostic pathways have been pioneered in

Denmark, with urgent referrals for both alarm symptoms and serious, non-specific symptoms (GP triage is required for the latter—with direct access to investigations) and the use of diagnostic centres (also with direct access) for vague symptoms [111]. Similar approaches have been adopted in Norway and Sweden [112, 113], and tested in England as part of the “Accelerate, Coordinate, Evaluate” (ACE) programme [114–116]. Informed by ACE results, the 2019 National Health Service (NHS) long-term plan stipulates the creation of Rapid Diagnostic Centres (RDCs). These will initially focus on cancers associated with non-specific symptoms, followed by wider implementation for all patients with suspected cancer, including self-referral for red flag symptoms [117, 118].

A key aspect of these new pathways is direct access to specialist tests and imaging, recognising evidence of health system factors (particularly GP gatekeeping) on cancer outcomes [119–121]. Earlier strategies in England already included specific investment on GP direct access to CT scans and flexible sigmoidoscopy [122, 123] and laboratory tests [124]. Nonetheless, substantial regional variation in access is acknowledged [125]. Wide variations are therefore likely in terms of access and availability of RDCs.

Use of Novel Biomarkers

There has been substantial research in the development of biomarkers other than FIT for the detection of CRC; these include proteins, volatile organic compounds, stool DNA and liquid biopsy (comprising circulating tumour cells and cell-free DNA) [126, 127]. The methylated *SEPT9* gene is a promising biomarker [128–131]. However, evidence is scarce for the primary care setting, and this makes clinical applicability uncertain because of spectrum effect/bias (variation in performance due to testing in different populations) [130, 132].

CONCLUSION

Primary care professionals have a vital role in the timely diagnosis of CRC. They can also help

with prevention through behavioural interventions aiming at lifestyle changes and facilitating informed CRC screening participation. Importantly, most patients will present in primary care with lower gastrointestinal symptoms before being diagnosed. Diverse symptomatology requires the use of different pathways to diagnosis; guidance is available to facilitate this. Diagnostic tests to triage patients are available, along with promising emerging tools. Further innovations are required to deal with an increasing need for diagnostic investigations.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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