Coloproctology

A Practical Guide

Martyn Evans
Mark Davies
Rhiannon Harries
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Second Edition

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Contents

1 Triage Optimisation in Patients with Symptoms Suspicious of Colorectal Cancer

Ian Bissett and Kai Sheng Saw

Abstract

Despite the advent of screening programmes, diagnosis for the majority of colorectal cancers (CRC) still follows a symptomatic presentation. Current approaches to assessment of patients with symptoms suspicious of CRC rely on subjective symptoms which are poor predictors of CRC diagnosis. Multiple practical challenges have also arisen as a result of excessive reliance on symptoms for diagnosis and triage. Current approaches have also overwhelmed health care resources without producing the expected benefits. Better ways of triaging patients with symptoms suspicious of CRC are needed. The principles of triaging are explored followed by an overview of the advantages and limitations of a number of current triaging approaches. The faecal immunochemical test (FIT) is a prime candidate to bring major practice change in how these patients are triaged. FIT offers practical solutions that address many of the challenges faced by current triaging methods. The role and evidence supporting the use of FIT in symptomatic patients is explored in detail, with further discussion about unresolved considerations such as safety netting for patients with low FIT results, equity concerns, and future directions for improving FIT implementation.

Keywords

Colorectal cancer • Faecal immunochemical test • Diagnostic triage • Symptomatic patients

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Key Points

- The specificity of symptoms in predicting CRC is very low.
- Primary investigations are invasive, resource intensive and associated with complications.
- In the majority of symptomatic patients, these investigations do not identify significant pathology.
- A triaging system that is more sensitive and specific than symptoms alone is needed.
- Multiple studies have demonstrated a high sensitivity and specificity for FIT testing in symptomatic patients.
- FIT testing offers the possibility of ruling out CRC in patients with very low FIT f-Hb levels and escalation of urgent colonoscopy in those with very high levels.
- Unanswered questions include the best method to identify those patients who should be referred directly for colonoscopy without FIT testing (particularly those with suspected inflammatory bowel disease) and the optimal safety-netting process to follow up those with very low f-Hb levels.

1.1 Introduction

As the third most common malignancy with an estimated 900,000 attributable deaths annually, colorectal cancer (CRC) is a significant public health concern worldwide [1]. Although more common in high-income countries, the incidence of CRC is increasing in low and middle-income countries due to increased life expectancy and the westernisation of society [1, 2]. Notably, there has also been a growing incidence of CRC in younger patients (<50 years) in high-income countries [3, 4].

Historically, healthcare providers have limited tools to diagnose CRC. Structural diagnostic tests have improved significantly since the days of barium enemas to the widely used colonoscopy and computed tomographic colonography (CTC) today. While the diagnostic utility of colonoscopy and CTC is obvious, these are relatively invasive diagnostic tests with limited patient acceptability and limited accessibility due to the intensive resources required to operate and maintain a high-quality diagnostic service. While stool based tests for diagnosis of colorectal cancer have been in existence for decades, it was not until the early 2000s when the faecal immunochemical test for haemoglobin (FIT) was widely adopted across Europe for CRC screening of asymptomatic patients.

The importance of early diagnosis of CRC by stage is well established. This is evidenced by the fact that despite high incidence rates, CRC related mortality in many high-income countries are decreasing, largely attributable to CRC screening programmes and to a lesser extent better treatment and surveillance [1, 4]. However, even in countries with established CRC screening programmes, the majority of CRCs are still diagnosed when suspicious symptoms are investigated. This is

crucial as the proportion of individuals with advanced stage CRC is higher in the symptomatic cohort than in those diagnosed in screening the asymptomatic population. Furthermore, a significant proportion of these patients are emergency presentations (>20%) with poor prognosis [5]. Many would have experienced prolonged presence of symptoms and delay to diagnosis [6, 7]. Hence, the need to optimise triage.

Diagnosis is often preceded by a complex sequence of events involving patients, healthcare providers and the health system. It is useful to consider theoretical models that describe the three phases of cancer in this context—the invisible asymptomatic phase, followed by the visible asymptomatic phase and then the symptomatic phase, generally indicative of more advanced disease stage [8]. This chapter primarily focuses on the timeframe between when patients first present to healthcare providers with symptoms suspicious of CRC and when a formal diagnosis is made. The chapter provides an evidence-based discussion around the utility and issues with using symptoms as a tool for diagnosis and various triaging approaches for patients with symptoms suspicious of CRC.

1.2 Symptoms Suggestive of Colorectal Cancer

The symptoms and signs that are associated with presence of CRC include rectal bleeding, change in bowel habit, weight loss, palpable abdominal or rectal mass and abdominal pain. While these common symptoms are often included in diagnostic guidelines, patients presenting with less common symptoms such as tenesmus, unexplained anorectal pain, urgency to defaecate etc. are not infrequently referred for further investigation as part of a cluster of symptoms due to concern about colorectal malignancy. Clinical symptoms of bowel obstruction or tumour perforation are often observed in patients with CRC who first present to emergency departments.

Despite the importance of symptoms in identifying potential cases of CRC, there are pitfalls associated with the excessive reliance on symptoms in contemporary diagnostic pathways. The following sections outline the main issues associated with symptoms, then explore how these features interact and lead to the current challenge of diagnosing CRC amongst symptomatic patients.

Many symptoms commonly associated with CRC such as change in bowel habit, weight loss, and abdominal pain, are prevalent in the general adult population. For instance, up to 10% of individuals experience a change in bowel habit, 3% experience weight loss, and 25% report abdominal pain [9]. Rectal bleeding, the symptom most strongly associated with CRC, is estimated to occur in up to 15% of adults during their lifetime and that only half of these patients seek consultation for these symptoms [9]. An increase in referrals for patients with symptoms suspicious of CRC has also been reported in recent years [9–11].

Symptoms, by definition, are subjective with variability in definition and interpretation among patients and health providers. The cited symptoms are often open to interpretation and lack reliability, accuracy and reproducibility [12, 13]. For

instance, the definition of "change in bowel habit" varies among different health jurisdictions, with some considering any change including either diarrhoea or constipation, while others, like the NICE guidelines, focus on looser or more frequent stools as the defining feature. Furthermore, there is doubt over whether health practitioners are following such definitions when using guidelines in day to day practice [14].

As medical practice is increasingly informed by quantifiable measurements such as biomarkers, the continued primary reliance on subjective symptoms is somewhat incongruous. Attempts to improve the quantification of symptoms using validated questionnaires for assessing abdominal or gastrointestinal symptoms have failed to gain broad usage [12, 13].

Importantly, despite substantial evidence demonstrating the limited predictive value of individual symptoms for diagnosing CRC, many clinicians and healthcare jurisdictions still rely heavily on symptoms in contemporary diagnostic pathways. Many of these symptoms have discriminatory abilities that are only slightly better than chance alone at detection of CRC and are notably more effective in detecting benign colorectal pathology [12, 13, 15]. These symptoms often concurrently lack sufficient sensitivity and specificity for detecting CRC in the modern era. Even rectal bleeding, which has demonstrated a more consistent association with CRC, only exhibits a sensitivity ranging from 17 to 46% and a specificity range of 52–98% in published meta-analyses [12, 13, 15]. Some symptoms such as abdominal pain actually appear to fare worse than a coin toss at predicting CRC yet these remain common reasons for referral [13]. Combining a number of symptoms does not necessarily improve diagnostic performance significantly either but will be explored in detail in subsequent sections [12, 13]. Diagnostic performance of symptoms was also not significantly different regardless of whether studies were conducted in primary or secondary care highlighting their inherent limitations regardless of the healthcare providers experience of expertise [12, 13]. The challenges of using symptoms may stem from the lack of a clear underlying pathophysiological link between CRC and its presenting symptoms. The reliance on symptoms is also hampered by the fact that these may only become evident with relatively advanced disease.

1.3 Current Challenges of Diagnosing Colorectal Cancer Amongst Symptomatic Patients

There are multiple practical challenges in providing diagnostic investigations for patients with symptoms suggestive of CRC.

1.3.1 Risks of Invasive Investigations

The current approach to managing patients with concerning symptoms often leads to investigation with an invasive procedure. Over half of these patient ultimately

demonstrate no organic pathology and have no changes in the therapeutic approach [14–20]. Invasive investigations such as colonoscopy and CTC are inevitably associated with risks including perforation (0.005–0.091%), bleeding (0.21–1.14%), sedation complications, fluid and electrolyte anomalies, bacteraemia and death [21–24]. The risk of all-cause mortality within 30 days following colonoscopy is reported at 0.007–0.07% [21–24]. Notably, major complications such as perforation and bleeding have been consistently shown to be more likely among symptomatic patients undergoing diagnostic colonoscopy [22–24].

While considered less invasive than colonoscopy, CTC is not risk free. Perforation rates for CTC range from 0.035–0.04% [25, 26]. CTC complications were also reported to be generally higher for symptomatic patients undergoing diagnostic CTC [25, 26]. Additionally, CTC is associated with an increased lifetime cancer risk due to the radiation dose [27].

1.3.2 Low Patient Acceptability

The acceptability of colonoscopy to patients is not as high as most clinicians believe. Non-attendance rates for colonoscopy can be as high as 15–48% in different contexts [28]. Patients consistently rank the discomfort and inconvenience of bowel preparation as the most challenging aspect of the colonoscopy or CTC process [28, 29]. Concerns about modesty, logistical barriers and competing health priorities are also common reasons for not attending a colonoscopy after referral [28, 29]. Cultural taboos also emerged as a persistent theme and may be more important barriers to specific subgroups of the population, particularly as equity in health outcomes in multicultural societies are increasingly discussed [28, 29].

1.3.3 Excessive Investigation and Low Value Healthcare

Over-investigation of symptoms can have unintended consequence, leading to increased usage of healthcare resources that do not directly address the patients' initial complaint [19, 30, 31]. Common examples include the detection of colonic polyps unrelated to the presenting symptoms and extra colonic incidental findings on CTC (up to 13% of cases) [13, 30, 32]. This precipitates a 'cascade effect' of additional investigations and procedures that add substantial morbidity and cost without addressing the patient's initial symptoms [30, 32].

The concept of low value healthcare has gained increasing prominence in recent years. Low value care can be described as the delivery of tests or interventions where evidence suggests it confers no or very little benefit to patients; where the risk of patient harm is in excess of potential benefit; or incurring of additional healthcare costs without proportional added benefits to patients [31, 33, 34]. Colonoscopy use for some symptomatic patients (e.g. constipation as the sole symptom) has been highlighted as an example of low value healthcare [33]. Low value endoscopy procedures have increased in incidence over time and not

only cause a waste of health resources but also present a significant potential for downstream harm to patients [31, 33, 35].

1.3.4 Opportunity Costs Associated with Reliance on Symptoms for Risk Assessment

a. Unjustified diagnostic delays

Treating large cohorts of patients with varying symptoms as if they share a uniform risk of undiagnosed CRC inevitably results in unjustified delays for evaluation for some individuals with genuine underlying CRC. With rising numbers of symptomatic patients seeking medical attention, existing symptom-based triaging methods lead to decreasing CRC yield from colonoscopy and increased likelihood of delayed diagnoses and associated opportunity costs for those harbouring true undiagnosed CRC [20].

b. Enforced suboptimal rationing

A common system level response to overwhelming referrals is to ration access based sub-optimally on blunt tools such as aggregate demographic data and unreliable symptoms-based referral criteria. For example, younger symptomatic patients (<50-year-olds) harbouring true undiagnosed CRC face increased barriers to access colonoscopy and increased risk of misdiagnosis despite emerging evidence of increasing incidence of early onset CRC [36, 37]. This further highlights the inadequacy of many current triaging approaches for patients with symptoms suspicious of CRC which inappropriately sacrifice certain groups with true pathology while large numbers of colonoscopies with unremarkable findings are performed.

c. Wider system level trade-offs

Almost universally, a lack of adequate colonoscopy capacity has led to a bottleneck in population level bowel screening programmes resulting in restrictions in screening programme parameters and prolonged rollouts [38]. Although stage shift through CRC screening is widely recognised as the most cost-effective approach to improving CRC related survival, screening programmes are often perceived as an optional extra rather than essential. This is prompted by the perceived ethical responsibility to prioritise symptomatic patients in spite of prevailing evidence showing poor association between CRC and symptoms [13, 38, 39]. Each additional healthcare professional and healthcare dollar dedicated to performing colonoscopy on every symptomatic patients, means fewer resources for other healthcare programs that have more robust evidence supporting their value to the population.

1.3.5 Supply and Demand Imbalance

The key health resource challenge faced as a result of current approaches to assessment of patients with symptoms suspicious of CRC ultimately boils down to imbalances in colonoscopy (or CTC) supply and demand.

The overwhelming demand for specialist consultations and structural diagnostic tests is already well-recognised with further increases expected on the horizon [20]. The problem of increasing demand is perhaps best documented in data from the United Kingdom and has led to an unsustainable demand for specialist services and structural diagnostic tests [10, 14, 20]. The COVID-19 pandemic enforced downscaling of clinical activity further strained services despite an apparent reduction in symptomatic referrals in the early stages of the pandemic [40]. Alarmingly, the yield of CRC diagnosed among referred symptomatic patients has progressively declined from 14 to 8% despite a 45% increase in referrals over the years [14, 20]. With CRC related outcomes still remaining poor, symptoms-based referral criteria were further loosened, this increased referrals by 78–100% [20]. The result was a reduced yield of CRC diagnosis to 3–9% without any significant improvement in CRC related outcomes [20]. Efforts to manage the large volume of referred patients by mandating faster treatment pathways such as the "two-week-wait pathway", largely based on re-categorisation of patients by age and symptoms, has been shown to have no effect on CRC detection yield or clinically important outcomes [10, 14]. Such efforts also fail to recognise and address the fundamental problem of overwhelming demand due to inaccurate patient selection [14]. Straight to test pathways were then adopted in the UK to address the pressures of meeting policy targets [41, 42]. These did not translate to demonstrable improvement in CRC detection yield, stage shift or mortality, because these efforts only shifted the burden, rather than addressing the overwhelming demand created by symptoms-based criteria [41, 42]. All these efforts led to significant pressures within the public health system with numerous reports attesting to the worsening of problems over time [10, 20]. In blunt terms, policy changes based on symptoms-based criteria resulted in increased healthcare workload and overwhelmed secondary and tertiary care resources at many levels without producing the expected increases in number of CRC diagnosed or more importantly, improvements in CRC related survival [10, 14, 20, 42].

Many publicly funded health jurisdictions are likely to be in a similar predicament. With the general trend of increasing public health messaging around CRC and associated symptoms, most health jurisdictions are likely to see more referrals as the "symptom iceberg" is progressively revealed. The United Kingdom for example, saw an increase of referrals by 62–77% when a concerted public awareness campaign about symptoms of CRC were conducted [10, 20]. There is clearly is a need to enhance patient selection and optimise triage methods for those with symptoms suspicious for CRC using novel approaches that address the demand for colonoscopy (or CTC).

A simplistic yet frequently presented view is that increasing the supply and investing to build additional colonoscopy capacity is the panacea for the aforementioned problem. The importance of increasing colonoscopy and CTC capacity is undeniable. However, such efforts in isolation are unlikely to address current challenges outlined here. Despite the increase of absolute numbers of colonoscopies and CTC in the past decade, many jurisdictions continue to be under significant resource constraints in delivering colonoscopies. Even in health settings with a predominantly fee-for-service model, there is difficulty in increasing colonoscopy capacity as the workforce is highly skilled and training is often prolonged [43–45]. This highlights underlying complexities of setting up and maintaining high quality, fit for purpose endoscopy units [43–45].

The presented evidence suggests that relying heavily on symptoms to guide whether, as well as who, when, and how to investigate patients is problematic. This approach leads to development of a very large pool of individuals with suspicious but loosely defined symptoms requiring colonoscopy or CTC to rule out CRC [46]. Imbalances in supply and demand for colonoscopy and CTC leads to rationing to cope with finite healthcare resources. In view of these shortcomings and the increasing presentations and referrals of patients with symptoms suspicious of CRC, there is an urgent need for better ways to triage symptomatic patients.

1.4 The Need for Triaging and Defining Optimum

Despite the acknowledged limitations of relying on symptoms for assessment of patients with symptoms suspicious of CRC, there will be ongoing demand for investigating and treating symptomatic patients. It is also improbable that there will be a viable alternative to colonoscopy as the gold standard for CRC diagnosis in the foreseeable future, especially an alternative that is less invasive, more accessible and easily scalable with equivalent diagnostic ability. With these fixed issues surrounding demand and supply, triaging seems to be the most practical solution forward in this context.

Triaging is the inevitable consequence of an imbalance between healthcare demand and resources [47]. The term was derived from the French word "trier", and was originally used to describe the sorting of agricultural products [47, 48]. First conceptualised in war time, the term is now used in many healthcare contexts and has a narrower definition in practice compared to other similar terms such as resource allocation and rationing [47].

Iserson and Moskop proposed three key features of any triaging system [47], namely

(i) At least moderate scarcity of resource.
(ii) A triaging plan based on set criteria to determine specific management and priority.
(iii) Triage plan execution by a health care worker (triage officer).

These conditions appear to apply fittingly to the context of assessment of patients with symptoms suspicious of CRC. The ethical values of importance of human life and justice are key principles in all triage systems but certain values such as patient or physician autonomy, physician–patient fidelity and ownership of healthcare resource are often deliberately not taken into account in the development and execution of triage plans [49].

Initially it is important to establish the clear primary goals of a triaging system before moving on to discussions about methods to optimise a triaging system to meet these goals. To illustrate, during war time, there are different doctrines that govern triaging of casualties with some clearly prioritising treatment of those most likely to return to the battlefield quickly in line with the primary goal of conserving fighting capability while other triage doctrines prioritise the treatment of critical treatable casualties in line with the contemporary goals of healthcare practice [47]. It is reasonable to assume that a shared primary goal for any diagnostic pathway for patients with symptoms suspicious of CRC would be the timely identification of as many cases of CRC a possible from the large pool of symptomatic patients requiring investigation.

'To optimise' is defined in the Oxford dictionary as "to make something as good as it can be". Who and what outcomes a triage system is optimised for can influence how a triage system is designed.

To illustrate:-

(i) From individual patients' and individual treating doctors' perspective, perhaps an optimal triaging system for patients with symptoms suspicious of CRC would aim to achieve the maximal sensitivity for CRC, whereby CRC detection is as good as it can. This would entail tolerating a high degree of false positives and resource expenditure to detect small numbers of additional CRC.

(ii) From a statistical and public health perspective, perhaps an optimal triaging system for patients with symptoms suspicious of CRC would aim to set a test positivity threshold at the point of maximal test sensitivity and specificity, whereby test efficiency is as good as it can be. This would imply tolerance of some false negatives as a trade off to achieve fewer false positives.

(iii) From a health economics perspective, perhaps an optimal triaging system for patients with symptoms suspicious of CRC would aim for maximal cost efficiency, whereby the overall costs are as low as it can be. This would imply that decisions are likely to be primarily driven by costs.

(iv) From a private health care provider perspective in a fee-for-service model, perhaps an optimal triaging system for patients with symptoms suspicious of CRC is biased towards approaches whereby revenues are as high as it can be for the healthcare institution.

(v) From a health equity perspective, perhaps an optimal triaging system for patients with symptoms suspicious of CRC is biased towards approaches whereby population subgroups who have historically poorer outcomes are further prioritised.

Clearly, it is difficult to recommend a single "correct" approach to triage optimisation in patients with symptoms suspicious of CRC. This will be influenced by the available evidence, societal values, available resources and other factors [47, 49].

The most practical approach would ideally involve all relevant stakeholders within a healthcare system, developing an optimal triage plan utilising the available evidence base with streamlined goals. In addition, policy makers should not lose sight of the need to improve availability of any resources that would reduce the need for triaging.

1.5 An Overview of Current Approaches to Triaging

If the presence of symptoms in individual patients is considered as the starting point in the health care journey of these patients, then it would be important to acknowledge that there is some degree of "self-triaging" by patients before they first present to seek medical care. Not all symptomatic patients seek medical care and those that do, do so at different stages [3, 4, 6, 19, 50]. Interventions in areas preceding formal contact with healthcare systems may be worth considering also. The recent availability of multipurpose technology such as smartphones and digital healthcare applications make this possible [51, 52].

At one end of the spectrum of conventional triaging approaches there are open access endoscopy units. This approach to investigating patients with symptoms suspicious of CRC does not technically involve a formal triaging system beyond what individual clinicians deem to be sufficient justification to accept a patient for colonoscopy on a case-by-case basis. This form of "triaging" is predominantly based on individual clinician judgement of risk of undiagnosed CRC based on a patient's symptoms. When colonoscopies performed in these settings are audited against established specialty society referral guidelines, 22–37% of performed colonoscopies are "generally not indicated", with higher yield of significant pathological findings among patients who met recommended referral criteria for colonoscopy [53–55]. The large number of issues that follow an approach based on symptoms alone have already been discussed. While there is an apparent need to improve upon such approaches in the modern era, in certain contexts, such as a fee-for-service funding model, there may be little incentive to change such approaches of "triaging" colonoscopy access for patients with symptoms suspicious of CRC [56].

The most common formal triaging approach for patients with symptoms suspicious of CRC is referral criteria-based triaging. The most well recognised referral criteria designed specifically for triaging of patients with symptoms suspicious of CRC is the National Institute for Health and Clinical Excellence (NICE) guidelines [57]. The NICE guidelines were first introduced in 2005 and has subsequently underwent multiple updates. Scottish Intercollegiate Guidelines Network (SIGN) referral criteria and many other locally implemented referral criteria for triaging symptomatic patients are derived from similar principles [58–60]. Broadly speaking, these triaging referral criteria attempt to sort symptomatic patients

by probability of undiagnosed CRC based upon contemporary understanding of various established risk factors. Most of these referral criteria place significant emphasis on presence of specific symptoms and age of the patient, in addition to some physical exam findings (e.g. palpable mass) and investigation findings (e.g. haemoglobin level). Acknowledging that individual symptoms alone are not particularly accurate at predicting risk of undiagnosed CRC, a combination of factors are often used as a criteria for specialist referral or further investigation. (See Table 1.1).

In the detection of CRC among symptomatic patients, the sensitivity for NICE referral criteria has been reported as 47–92% and specificity as 42–71% depending on study methodology [18, 19, 61, 62]. Similarly for SIGN referral criteria a sensitivity of 43–83% and specificity of 43%-69% has been reported [18, 62] This triaging approach fulfils the three features of triaging systems outlined previously and many publicly funded healthcare systems officially implement this approach currently [47] Triaging with symptoms-based referral criteria is more systematic with reasonable diagnostic performance. However, this approach has not overcome the challenges associated with triaging based solely on symptoms.

Multivariable risk assessment tools have been developed to further optimise triaging of patients with symptoms suspicious of CRC. This approach generally utilises weighted risk factors based on mathematical analysis of patient databases to produce a summative probability of undiagnosed CRC. An early example of such a triaging approach was the Weighted Numerical Score (WNS) [63]. The WNS algorithm was developed from prospectively collected data and subsequently validated in external populations [19, 63, 64]. Discriminatory ability (area under receiver-operator characteristic curve, AUROC) of the WNS was reported at 0.86 and has been consistently high in subsequent validation studies [19, 63, 64]. The WNS has been shown to be similar in sensitivity for CRC detection but had higher specificity when compared with contemporary symptoms-based referral criteria [19, 64]. Some other examples of multivariable risk assessment tools that also combine a variety of demographic, medical history, symptoms, signs and investigation data mathematically include the QCancer® model, The Cancer Prediction in Exeter Score (CAPER Score) and the Bristol-Birmingham (BB) equation [64]. The majority of these multivariable risk prediction algorithms have also been reported to have high AUROC and better overall diagnostic performance when compared to contemporary symptoms-based referral criteria [19, 64]. However, it is unclear if the WNS is in widespread use since it was first published [63]. Other risk calculators have not achieved widespread use nor have they been endorsed officially by reputable institutions for routine triaging of symptomatic patients despite the significant challenges in managing demand for colonoscopy. While the role of publication bias is unclear, limited evidence of external validity for the majority of these risk assessment tools likely limits their widespread implementation [64]. The majority of these risk assessment tools also appear to still be bounded by a paradigm that relies heavily on symptoms for prediction of CRC, as observed in

Table 1.1 Table comparing NICE, SIGN and New Zealand symptoms based triaging referral criteria for patients with symptoms suspicious of CRC

2011 NICE guidance (CG27)	2015 NICE guidance (NG12)	2017 NICE guidance (DG30)	SIGN 126 (2016)	New Zealand referral criteria for direct access outpatient colonoscopy or computed tomography colonography (2019)
• Age ≥ 40 years + rectal bleeding + change in bowel habit persisting ≥ 6 weeks • Age ≥ 60 years + rectal bleeding persisting ≥ 6 weeks without a change in bowel habit and without anal symptoms • Age ≥ 60 years + change in bowel habit persisting ≥ 6 weeks without rectal bleeding • Patients presenting a right lower abdominal mass consistent with involvement of the large bowel • Patients presenting with a palpable rectal mass • Patients with unexplained iron deficiency anaemia	• Age > 40 + unexplained weight loss + abdominal pain • Age > 50 + unexplained rectal bleeding • Age > 60 + • iron-deficiency anaemia or • changes in their bowel habit • Rectal or abdominal mass • Aged < 50 + rectal bleeding + any of the following unexplained symptoms or findings: • abdominal pain • change in bowel habit • weight loss • iron-deficiency anaemia	Adults without rectal bleeding and • Age > 50 and + • abdominal pain or • weight loss, or • Age < 60 + • changes in their bowel habit or • iron-deficiency anaemia, or • Age > 60 + • anaemia even in the absence of iron deficiency	• Patients > 40 years old + • Persistent rectal bleeding without anal symptoms • Persistent change in bowel habit (> 6 weeks) • Persistent diarrhoea • Significant family history • Right-sided abdominal mass • Palpable rectal mass • Unexplained iron deficiency anaemia	**Two-week category** • Known or suspected CRC (on imaging, palpable/visible on rectal exam) • Unexplained rectal bleeding (benign anal causes treated or excluded) + iron deficiency anaemia • Altered bowel habit (looser/more frequent) > 6 weeks + unexplained rectal bleeding (benign anal causes treated or excluded) + Age ≥ 50

(continued)

Table 1.1 (continued)

2011 NICE guidance (CG27)	2015 NICE guidance (NG12)	2017 NICE guidance (DG30)	SIGN 126 (2016)	New Zealand referral criteria for direct access outpatient colonoscopy or computed tomography colonography (2019)
				Six-week category • Altered bowel habit (looser/more frequent) > 6 weeks + Age ≥ 50 • Altered bowel habit (looser/more frequent) > 6 weeks + unexplained rectal bleeding (benign anal causes treated or excluded) + Age 40–50 • Unexplained rectal bleeding (benign anal causes treated or excluded) + Age ≥ 50 • Unexplained iron deficiency anaemia • New Zealand Guidelines Group Category 2 family history + one or more of altered bowel habit (looser/more frequent) > 6 weeks + unexplained rectal bleeding (benign and anal causes treated or excluded) + Age ≥ 40 • New Zealand Guidelines Group Category 3 family history + one or more of altered bowel habit (looser/more frequent) > 6 weeks + unexplained rectal bleeding (benign and anal causes treated or excluded) + Age ≥ 25 • Suspected/assessment inflammatory bowel disease (consider specialist assessment at clinic)

(continued)

Table 1.1 (continued)

2011 NICE guidance (CG27)	2015 NICE guidance (NG12)	2017 NICE guidance (DG30)	SIGN 126 (2016)	New Zealand referral criteria for direct access outpatient colonoscopy or computed tomography colonography (2019)
				Not accepted • Acute diarrhoea < 6 weeks' duration • Rectal bleeding + Age < 50 • Constipation as a single symptom • Abdominal pain alone without any 'six-week category' features • Decreased ferritin + Age < 50 years with normal haemoglobin • Abdominal mass • Metastatic adenocarcinoma unknown primary • Irritable bowel syndrome

the retention of significant weighting for symptoms in many of these mathematical formulations [64]. In addition, symptoms can still be interpreted inconsistently prior to incorporation into risk assessment tools [65].

Another increasingly explored approach to optimise triaging of patients with symptoms suspicious of CRC is through the use of molecular biomarkers. Serum haemoglobin and iron are the biomarkers most clinicians are familiar with and have already been incorporated into many referral criteria-based triaging. The sensitivity of anaemia is estimated to range from 13 to 68% with specificity estimated to range from 83 to 92% [12, 15, 61]. The relatively poor sensitivity and high specificity suggests anaemia is likely a late indicator of CRC even among symptomatic patients. Nevertheless, anaemia appears to rank highly with increased importance over most symptoms in many referral criteria-based triaging. (See Table 1.1) A number of available multivariable risk assessment tools for triaging of patients with symptoms suspicious of CRC have also incorporated data on serum haemoglobin, as well as other biomarkers [64].

In principle, biomarkers are often objectively quantifiable and reliably reproduced. These characteristics make biomarkers attractive candidates for research and implementation in modern clinical practice. While interpretation of biomarker data is context specific and often debated, the use of objectively quantifiable and reproducible biomarkers form a better starting point in building a reliable evidence base that supports data-driven practice change. It is therefore encouraging to see increasing research in this area, with a wide range of serum, stool and urine based molecular biomarkers for the detection of CRC being explored in recent years [66, 67]. Examples of biomarkers that have been explored specifically for use for detection of CRC among symptomatic patients include faecal calprotectin, faecal M2-PK, faecal DNA and RNA, serum YKL-40, serum CEA, serum TIMP-1 and urinary volatile organic compound [19, 66–73]. While some such as faecal calprotectin and serum CEA have been shown to have limited diagnostic performance for detection of CRC in symptomatic patients, many biomarkers remain in the early stages of investigation [19, 66, 67, 70, 74]. Of the explored biomarkers, the prime molecular biomarker candidate that is most likely to cause large scale practice change against the backdrop of current challenges in triaging patients with symptoms suspicious of CRC, is faecal haemoglobin.

1.6 The Faecal Immunochemical Test (FIT)

FIT is essentially a test to detect occult human haemoglobin (f-Hb) in faeces. While the same immunochemical technology is also being used to detect other molecules in human faeces, the majority of existing evidence about FIT refers specifically to the detection of faecal haemoglobin [75, 76]. While testing for occult blood to detect colonic pathology is not a new concept, FIT represents a substantial technological improvement compared to historical chemical based techniques for faecal haemoglobin detection such guaic faecal occult blood tests [77, 78]. Hence, the widespread use of the term FIT was encouraged by the

World Endoscopy Organisation to clearly distinguish a new generation of immunochemical based faecal haemoglobin tests with significantly improved diagnostic performance [77].

Previous techniques for faecal occult blood detection were based primarily upon the pseudo-peroxidase activity of the haem moiety of haemoglobin [66, 78]. The limitations of such chemical based techniques are well documented [66, 78–80]. FIT utilises antibodies specific for the globin moiety of human haemoglobin [78]. These antibodies are bound to carrier particles such as polysaccharide, latex or gold [78]. When present in faeces, human globin binds to these antibodies, forming small antibody-globin aggregates in the process [78]. A variety of immunoassay methods such as immunochromatography and immunoturbidometry are then used to measure the development of these antibody–globin complexes [78]. These differences in immunoassay methods give rise to the two broad categories of FIT—qualitative FIT based on immunochromatography and quantitative FIT based on immunoturbidometry [78]. There are important differences in diagnostic performance between qualitative and quantitative techniques [78, 79, 81]. While used extensively in some health jurisdictions, there are important limitations with regards to the reliability of diagnostic performance estimates, impact on clinical outcomes and transferability of results between different qualitative FIT kits [66, 79, 82]. Our focus in the subsequent paragraphs will be on quantitative FIT as this method is endorsed by many international institutions and has already achieved widespread adoption, particularly in CRC screening, due to the greater potential to leverage f-Hb data to meet clinical or logistical requirements [78, 79].

All commercially available FIT kits are non-invasive and suitable for usage by patients at home [79, 80]. Currently available kits are often specifically designed to be fairly simple to use even for the inexperienced [79, 80]. The widespread adoption of FIT in screening programmes and generally low rate of spoiled kits is a testament to the ease of use for patients [80].

For perspective, FIT is not exactly new technology. Immunochemical techniques for detection of blood in faeces was first described in 1978 [83]. Over time, refinements in technique improved specificity for human blood [78, 84]. Experts at the time proposed that immunochemical techniques for detection of blood in faeces could be applied in various clinical contexts for detection of CRC such as in screening, surveillance and also among symptomatic patients [83]. Curiously, FIT has only achieved widespread adoption in the context of screening asymptomatic patients to date [80, 85].

In the early 1990s, FIT was widely adopted across Japan for CRC screening [84]. FIT was first piloted for population based screening in Italy in 1996 and has since been a cornerstone for many CRC screening programmes in the world [84–86]. Most of the current evidence about FIT use is in the context of asymptomatic patients.

While it is has been clear that faecal haemoglobin levels detected by FIT have well-established associations with neoplasia-related bleeding in the colon, it was not until the early 2010s when a number of research groups examined the utility of

FIT in the context of symptomatic patients [79, 80, 87]. A systematic review commissioned by NICE led to recommendation of FIT use as part of the updated NICE diagnostic guidelines for assessment of patients with symptoms suspicious of CRC for the first time [57, 87]. This change in guidelines, alongside further restriction of access to endoscopy services due to the COVID-19 pandemic, resulted in an explosion in the number of publications related to the use of FIT among symptomatic patients to detect CRC in the past few years [88, 89]. As will be demonstrated in the subsequent paragraphs, when used as a triaging tool in patients with symptoms suspicious of CRC, FIT appears to be an enticing option as it offers practical solutions that address many of the challenges faced by current methods of triaging outlined above.

The first practical question on many clinicians' minds is likely related to the diagnostic performance of FIT for the detection of CRC when used to triage patients with symptoms suspicious of undiagnosed CRC. From 2017 to 2022, there were six meta-analysis on the utility of FIT as a triaging tool for assessment of symptomatic patients [87–92]. (See Table 1.2) Despite changes in the number of included studies over the years and variations in meta-analysis inclusion and exclusion criteria, all meta-analyses came to a remarkably similar conclusion that FIT is suitable for use as a triaging tool in patients with symptoms suspicious of CRC.

Most meta-analyses focused heavily on the controversial but potentially practice changing question of the utility of FIT as a "rule-out" test for CRC. Westwood et al. first showed in 2017 that at the positivity threshold of 10 μg Hb/g faeces, summary sensitivity for CRC detection was 92.1% with all included studies reporting negative predictive values > 99% [87]. Two recent meta-analyses published in 2022 have similarly demonstrated summary sensitivities of 88.7%-91.0% at the positivity threshold of 10 μg Hb/g faeces [88, 89]. Despite the significant increase in number of included studies resulting in total cohort sizes of up to 36,000 patients in recent meta-analyses, negative predictive values at the positivity threshold of 10 μg Hb/g faeces remained consistently above 99% with reported negative likelihood ratio of 0.14 [88, 89]. When positivity thresholds were set at the lower limit of detection, the ability for FIT to "rule-out" CRC improves even further, with suggestions that FIT diagnostic performance actually approaches commonly quoted sensitivity of the gold standard, colonoscopy, itself [88, 89, 93]. There are technical questions regarding the appropriateness of utilising the lower limit of detection of FIT clinically, hence most discussions about FIT as "rule-out" test focus on the positivity threshold of 10 μg Hb/g faeces [46, 94]. Nevertheless, these diagnostic performance parameters strongly suggest that, at very low faecal haemoglobin positivity thresholds, FIT is an acceptable "rule-out" test for CRC amongst symptomatic patients.

The diagnostic performance of quantitative FIT is variable depending on positivity threshold [78–80]. This is succinctly illustrated in Fig. 1.1 which demonstrate summary receiver operating characteristic curves for FIT at various positivity thresholds [89] (See Fig. 1.1).

This characteristic of quantitative FIT can be exploited to maximise the utility of FIT as a triaging tool. An example is to use FIT as a "rule-in" test to

Table 1.2 Table comparing meta-analyses of FIT diagnostic accuracy for CRC detection at various positivity thresholds

FIT as a "RULE-OUT" Test						
Meta-analysis	Publication year	N	Threshold	Summary sensitivity	Summary specificity	Summary negative likelihood ratio
Lower limits of detection						
Pin Vieito et al.	2021	41,338	> 2–7 μg Hb/g faeces	93.4% (88.0–96.4%)	76.9% (67.7–84.0%)	0.09 (0.05–0.15)
Saw et al.	2022	10,624	2 μg Hb/g faeces	96.8% (91.0–98.9%)	65.6% (59.0–71.6%)	0.08 (0.04–0.17)
Booth et al.	2022	26,056	> 2–4 μg Hb/g faeces	94.7% (90.5–97.1%)	66.5% (58.7–73.6%)	Not stated
10 μg Hb/g faeces						
Westwood et al.	2017	4091	10 μg Hb/g faeces	92.1% (86.9–95.3%)	85.8% (78.3–91.0%)	Not stated
Pin Vieito et al.	2019	4035	10 μg Hb/g faeces	94.1% (90.0–96.6%)	66.0% (47.1–80.9%)	0.09 (0.06–0.14)
Stonstreet et al.	2019	4096	10–15 μg Hb/g faeces	93.0%* (88.0–96.0%)	87.0% (83.0–90.0%)	0.12 (Not stated)
Pin Vieito et al.	2021	48,872	10 μg Hb/g faeces	87.2% (81.0–91.6%)	84.4% (79.4–88.3%)	0.15 (0.10 to 0.22)
Saw et al.	2022	25,500	10 μg Hb/g faeces	88.7% (85.2–91.4%	80.5% (75.3–84.8%)	0.14 (0.12 to 0.18)
Booth et al.	2022	35,945	10 μg Hb/g faeces	91.0% (88.9–92.7%)	75.2% (69.6–80.1%)	Not stated
FIT as a "RULE-IN" Test						
Meta-analysis	Publication year	N	Threshold	Summary sensitivity	Summary specificity	Summary positive likelihood ratio
100 μg Hb/g faeces						
Saw et al.	2022	5593	100 μg Hb/g faeces	68.1% (59.2–75.9%)	93.4% (91.3–95.1%)	10.2 (7.2–14.4)
150 μg Hb/g faeces						
Pin Vieito et al.	2021	34,691	150 μg Hb/g faeces	64.1% (57.8–69.9%)	95.0% (91.2–97.2%)	12.7 (7.7–21.1)
Saw et al.	2022	10,375	150 μg Hb/g faeces	66.3% (52.2–78.0%)	95.1% (93.6–96.3%)	13.1 (11.7–14.5)