Colorectal cancer diagnosis: Pitfalls and opportunities

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Abstract

Colorectal cancer (CRC) is a major health problem in the Western world. The diagnostic process is a challenge in all health systems for many reasons: There are often no specific symptoms; lower abdominal symptoms are very common and mostly related to non-neoplastic diseases, not CRC; diagnosis of CRC is mainly based on colonoscopy, an invasive procedure; and the resource for diagnosis is usually scarce. Furthermore, the available predictive models for CRC are based on the evaluation of symptoms, and their diagnostic accuracy is limited. Moreover, diagnosis is a complex process involving a sequence of events related to the patient, the initial consulting physician and the health system. Understanding this process is the first step in identifying avoidable factors and reducing the effects of diagnostic delay on the prognosis of CRC. In this article, we describe the predictive value of symptoms for CRC detection. We summarize the available evidence concerning the diagnostic process, as well as the factors implicated in its delay and the methods proposed to reduce it. We describe the different prioritization criteria and predictive models for CRC detection, specifically addressing the two-week wait referral guideline from the National Institute of Clinical Excellence in terms of efficacy, efficiency and diagnostic accuracy. Finally, we collected information on the usefulness of biomarkers, specifically the faecal immunochemical test, as non-invasive diagnostic tests for CRC detection in symptomatic patients.

Key words: Colorectal cancer; Colonoscopy; Primary health care; Faecal immunochemical test; Diagnostic yield; Diagnostic accuracy; Risk stratification; Open endoscopy unit; Practice guidelines; Health plan implementation

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Core tip: In this review, we summarize the pitfalls in the diagnostic procedure for colorectal cancer (CRC) in symptomatic patients. We collected the available information concerning the value of symptoms as predictors of CRC and the factors involved in the delay of CRC diagnosis, including those related to the patient, to the physicians and to hospital delay. In this way, we review the currently available sets of appropriateness criteria for colonoscopy in symptomatic patients, the prioritization criteria and predictive models for CRC detection and, finally, the role of available biomarkers in
Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death. In Western Europe, it is the seventh leading cause of death, the fourth leading cause of loss of life expectancy, and it is associated with an elevated consumption of resources. The stage of the tumour at the time of treatment is considered the most important predictor of survival. Thus, in Europe, survival is 93% after 3 years for Duke stage A tumours, but it is only 16% after 3 years for stage D tumours. Two strategies are widely used to improve CRC prognosis and to optimize the health resources consumed: Population-based CRC screening programs and early diagnosis strategies in symptomatic patients. Population-based screening programs in asymptomatic patients have been demonstrated to reduce the incidence and mortality rates of CRC in two ways: Removing preneoplastic lesions with polypectomy and diagnosing a higher proportion of CRCs at an early stage.

On the other hand, the early diagnosis of CRC in symptomatic patients remains a problem. It is a complex process that begins when the patient detects the first symptoms until a diagnostic procedure is performed, undergoing a consultation with a general practitioner, a referral to the specialist, and the waiting period for diagnostic procedures, such as colonoscopy. All this contributes to the perception that delay in CRC diagnosis is a multifactorial problem. In the general population, lower abdominal symptoms are very common and are a frequent cause of visits to the general practitioner. The issue is that symptoms are usually very vague and non-specific, with a poor sensitivity for CRC. In most cases, these symptoms are produced by benign, self-limiting illness, contributing to the patient’s delay in seeking help and the practitioner’s delay in referring the patient to a specialist. Moreover, the growing demand for colonoscopy has become a significant problem, as endoscopic resources are limited; these waiting periods also delay the diagnosis of CRC. Computed tomography (CT) colonography could be an alternative, especially in elderly patients with poor specific symptoms such as abdominal pain or weight loss. However, the referral rate for additional tests after CT-colonography must be reduced to avoid the potential to increase anxiety and overall cost. For these reasons, as colonoscopy is the gold standard for CRC investigation, several risk classification scores based on symptoms have been developed to determine which patients are most at risk of having CRC and thus to reduce the delay between the initial consultation and the colonoscopy.

The objective of this article was to review the pitfalls and missed opportunities in the process of CRC diagnosis in symptomatic patients. First, we evaluated the evidence concerning the value of symptoms as predictors of colorectal neoplasia. We showed the effect of delayed diagnosis on CRC prognosis as well as the factors related to this delay. This includes factors related to the patient, to the first attending physician (most likely in a primary setting), and, finally, to the hospital delay as a result of the waiting period before colonoscopy. We analysed the available sets of criteria for colonoscopy diagnosis in symptomatic patients, along with the prioritization criteria and the predictive scores for CRC diagnosis and their diagnostic yield for CRC. Finally, we explored the usefulness of the available biomarkers to determine the types of patients who can benefit the most from a colonoscopy.

VALUE OF SYMPTOMS

In the general population, abdominal symptoms account for up to 10% of consultations with general practitioners. Most of these symptoms are related to chronic functional conditions (irritable bowel syndrome, chronic constipation) or anorectal benign lesions that do not benefit from colonoscopy evaluation. In clinical practice, it is common to perform a colonoscopy in patients with bowel symptoms due to the suspicion of CRC. In fact, many practice guidelines suggest that colonoscopy should be performed for bowel symptoms, but the importance and value of symptoms as indicators of CRC is not well established. While some reports suggest that symptoms may be useful in identifying CRC, others have found no such association. Moreover, few of these studies are recent and the perception of symptoms may have changed since the early studies were conducted.

Recently, several meta-analyses have analysed the risk of detecting CRC according to the symptoms reported. Ford et al. performed a systematic review and meta-analysis to assess the diagnostic accuracy of alarm features in predicting CRC. They included fifteen studies evaluating 19443 patients, with a pooled 6% CRC prevalence. CRC diagnosis was based either on colonoscopy (8), sigmoidoscopy (1), double contrast barium enema (1), or both lower endoscopy or barium enema (5). They included 1 population-based study, 11 secondary healthcare level studies, 2 primary healthcare level studies and 1 mixed levels study. In summary, the pooled sensitivity of the symptoms was poor (5% to 64%), but specificity was 95% for dark red rectal bleeding and abdominal mass (Figure 1). It is remarkable that both positive and negative likelihood ratios (PLR and NLR) lie close to 1; thus, the presence or absence of symptoms does not significantly modify...
Astin et al. [23] performed an additional systematic review and meta-analysis to identify the risk of CRC in patients reporting a symptom to a primary care provider. They included 23 studies that recruited 81464 participants. They analysed both single and paired symptoms. Positive predictive values (PPVs) for rectal bleeding from 13 papers ranged from 2.2% to 16% with a pooled estimate of 8.1%, and PLR ranged between 1.09 and 10.13 with a pooled estimate of 5.31. Pooled PPV estimates for other symptoms were: Abdominal pain (three studies), 3.3%; and anaemia (four studies), 9.7%. For rectal bleeding accompanied by weight loss or change in bowel habits, pooled PLRs were 1.9 and 1.8, respectively. Conversely, the PLR was one or less for abdominal pain, diarrhoea, or constipation accompanying rectal bleeding. The authors concluded that the investigation of rectal bleeding or anaemia in primary care patients is warranted, irrespective of whether other symptoms are present.

Additionally, Jellema et al. [24] performed a meta-analysis to summarize the available evidence concerning diagnostic tests that might help primary care physicians to identify patients with an increased risk for CRC among those consulting for non-acute lower abdominal symptoms. The tests evaluated included signs, symptoms, referral criteria, blood and faecal tests. With respect to symptoms (Table 1), sensitivity ranged between 13% and 51% and specificity ranged between 59% and 89%. As a result, the risk of detecting a CRC was not modified significantly between those patients with symptoms (PPV ranging between 6% and 14%) and those without any of the symptoms evaluated (1-negative predictive value, NPV, ranging between 3% and 10%). In contrast, the variable age (> 50 years) was more sensitive than any of the symptoms (91%), although the specificity was lower (36%), significantly modifying the risk of CRC detection between patients older and younger than 50 years (10%, 2%). Therefore, the value of symptoms for CRC detection is very poor. Symptoms alone are not adequate to establish a suspicion of CRC and they must be synthesized with other variables, such as demographic variables and analytical data.

**DELAY IN CRC DIAGNOSIS**

The period of time from the first symptoms until a final diagnosis is achieved can vary. In a recently published study, the median interval between symptoms and diagnosis was 128 d with a wide interquartile range (57.5-257.5). This interval was due to the delay from the first symptom until the initial consultation (19 d, interquartile range 3-83) and the delay in health service (66 d, interquartile range 25-159) (Figure 2) [25]. There is a controversy regarding the association between diagnostic and therapeutic delay and the prognosis of CRC. In fact, there seems to be a lack of association between diagnostic delay, CRC survival and stage [26], suggesting that, in CRC, the symptomatic phase is only a small component of the natural history of the disease. When colon and rectal cancer are analysed separately, an opposite association exists. For the colon, a greater delay is associated with an earlier stage at diagnosis,
Factors related to patient delay

As previously mentioned, lower abdominal symptoms are very common and mostly due to benign, self-limited conditions. Moreover, most are very vague and patients do not relate them to a serious illness. In the complexity of the process of cancer diagnosis, Andersen’s Model of Total Patient Delay[^28,^29], a theoretical framework, defines five time intervals in the decision-making process: Appraisal delay (time between the detection of symptoms and inferring illness), illness delay (period when the patient contemplates between consulting a medical practitioner or self-treating the illness); behavioural delay (delay in making an appointment with the general practitioner (GP)), scheduling delay (time elapsed between making an appointment and the first medical consultation) and treatment delay (until the initiation of treatment). Factors related to the patient are encompassed in the first four time intervals.

Many studies have focused on determining the causes that lead to a delay in seeking medical help once the patient notices the first symptoms, including factors that would increase the delay and others that would reduce it. These factors are listed in Table 2. Most of the studies show that the main factors associated with patient delay are the lack of knowledge and concern about potential risks associated with the symptoms as well as non-recognition of the seriousness of the symptoms[^28,^29], suggesting that appraisal delay is the main contributor to the global delay related to the patient[^30]. This situation entails a misinterpretation of symptoms, attributing them to a benign disease or assuming that they are part of the ageing process. In this way, non-recognition of the seriousness of symptoms will also lead to self-diagnosis, "wait and see" strategies and self-treatment.

Other important factors described in studies are those related to denial and fear of symptoms[^32]. They include fear and denial of cancer, fear of poor prognosis, or fear of embarrassing and unpleasant investigations, which are all related to a lack of adequate information. With respect to the symptoms, patients who suffer from persistent or more serious symptoms affecting the person's daily life, such as pain, vomiting or obstruction, delayed seeking treatment less often. In contrast, more common symptoms, such as changes in bowel habits, rectal bleeding, or nonspecific symptoms were associated with more prolonged delays. A recent study that examined medical-advice-seeking behaviours showed that one in five persons experiencing rectal bleeding or changes in bowel habits did not seek medical advice. Moreover, among those seeking help for rectal bleeding or changes in bowel habits, up to 18% and 37%, respectively, delayed seeking treatment by more than 1 month[^33]. There is no clear evidence of the way in which factors such as age, gender, marital

| Index test                    | Sensitivity | Specificity | PPV 1-NPV |
|------------------------------|-------------|-------------|-----------|
| Age (> 50)                   | 91%         | 36%         | 10% 2%    |
| Sex (male)                   | 62%         | 55%         | 13% 3%    |
| Family history               | 16%         | 91%         | 6% 4%     |
| Weight loss                  | 20%         | 89%         | 9% 6%     |
| Abdominal pain               | 35%         | 59%         | 5% 7%     |
| Rectal bleeding              | 44%         | 66%         | 7% 4%     |
| All bleeding, dark blood     | 35%         | 85%         | 14% 5%    |
| All bleeding, mixed with stool | 51%     | 71%         | 6% 3%     |
| Change in bowel habits       | 52%         | 61%         | 9% 4%     |
| Diarrhoea present            | 20%         | 73%         | 6% 10%    |
| Constipation                 | 13%         | 72%         | 6% 9%     |
| Two week rule positive       | 92%         | 42%         | 14% 3%    |
| Iron deficiency anaemia      | 13%         | 92%         | 13% 8%    |
| Faecal occult blood test positive | 75% | 86%         | 28% 1%    |
| Chemical                     | 95%         | 84%         | 21% 0%    |

The results are expressed as medians or pooled estimates. Adapted from Jellema *et al.*[^25]. PPV: Positive predictive value; NPV: Negative predictive value.

and for the rectum, a smaller delay is associated with an earlier stage[^26]. This could be explained because rectal cancer has well-defined symptoms, such as rectal bleeding with or without changes in bowel habits, while colon cancer-related symptoms are very vague at the onset, and when the seriousness of symptoms require investigation, the disease is more advanced[^27].

Table 1  Summary of findings (sensitivity, specificity, predictive values) for diagnostic tests for colorectal cancer detection evaluated by at least four primary diagnostic studies

![Figure 2 Distribution of delay intervals in colorectal cancer diagnosis (in days).](image-url)
status, socioeconomic status and education level impact delay. Some studies have shown that males and younger people tend to delay more often. Additionally, low socioeconomic status and low educational level seem to be associated, but results are not consistent. In contrast, social support and a trustful relationship with the general practitioner are strongly associated with less delay,[25,34]. Finally, increased knowledge about CRC improves timely help-seeking for symptoms, reducing negative perceptions[35].

In sum, the main factors related to patient delay are caused by the lack of knowledge about symptoms, the importance and implications of CRC diagnosis at an early stage, and the diagnostic tools available. Therefore, an effort to educate the general population about CRC is warranted and may help to reduce delay.

Factors related to practitioner delay

One of the steps in the complex process of CRC diagnosis involves the physician that first sees the patient, usually the general practitioner. He must suspect that the symptoms are due to CRC and refer the patient for further investigations. Many factors are associated with practitioner delay (Table 3). Mitchell et al.[36] performed a systematic review including twenty-nine papers that considered factors that influenced practitioner delay. He described two main factors associated with an increase in delay, as both were considered to be factors in most of the studies included (≥ 75%)[30]. The first was initial misdiagnosis, either through prescribing symptomatic treatment or attributing symptoms to other benign conditions. In fact, missed opportunities to diagnose CRC before endoscopic referral occur in 31%-34% of patients presenting with symptoms, entailing an average delay from the first visit > 200 d. Among those patients, there was a mean of 2.41-4.2 missed opportunities. Those patients tended to be older and with more co-morbidities, including congestive heart failure or coronary artery disease. The main diagnostic key was iron-deficiency anaemia, which was associated with the longer delay to referral (> 300 d)[36,37].

The second main factor was failure to examine or investigate. Studies showed a frequent lack of physical examination among patients with lower abdominal symptoms, especially digital rectal examination[30]. In two recent studies, only 25% of patients with rectal carcinoma had a digital rectal examination at their first visit[11], and GPs only performed a physical examination of one in three patients[25]. These results are in accordance with previous studies that showed no improvement over time[38,39].

The available results on the effect of age and co-morbidities on delay are conflicting. Although previous studies have noted that elderly patients and those with co-morbidities are referred earlier[20], recent studies suggest the opposite, with more missed opportunities and more delay[36,37,40]. Moreover, psychiatric diseases are also associated with referral delay by the GP[40,41].

Regarding the consultation pattern, a greater interval to diagnosis was observed for patients with an increasing number of visits to the GP due to symptoms related to CRC and those lacking continuity of care[25,42]. Inaccurate or inadequate tests and a negative or a false negative test result increased the delay time[30].

Another important aspect is how the physician performs the request or referral. When the referral is urgent, includes three diagnostic clues, mentions the suspicion of CRC or contains documentation of verbal contact, the delay decreases[25,43]. Furthermore, the use of referral guidelines and the appropriate use of urgent referrals seems to reduce delay[44,45]. Studies have shown that strategies based on training primary
In the next section, we will evaluate the prioritization criteria and diagnostic indexes. Prioritization criteria or predictive indexes and diagnostic biomarkers.

**PRIORITIZATION CRITERIA AND CRC PREDICTIVE INDEXES**

Strategies for the early diagnosis of CRC in symptomatic patients may improve prognosis. In this regard, several risk classification scores based on symptoms have been developed. These classification criteria are intended to determine which patients are most at risk of having CRC, and thus to reduce the delay between the initial consultation in primary care settings and the colonoscopy. The two-week wait (TWW) referral guideline was introduced by the National Health System (NHS) and updated to its most recent version in 2011 (Table 4) by the National Institute of Clinical Excellence (NICE). It has been the most widely used and evaluated diagnostic criteria. Some other referral guidelines have recently been proposed and validated. Moreover, several CRC predictive indexes based on clinical symptoms have been proposed.

The TWW emerged in 2000 in response to the low survival rate at 5 years for CRC in Britain compared to other European countries with similar economic resources. The NHS established a prioritization system based on signs and symptoms associated with a high probability of detecting a CRC. Those patients who met any of these criteria should be assessed within 14 d of their referral. The NHS expected that up to 90% of incident CRC would be diagnosed through the TWW. It has been widely implemented across the NHS. Several articles have been published evaluating the efficacy, efficiency and diagnostic accuracy of the TWW. The TWW was implemented in most NHS centres; however, compliance with the guidelines has been poor. This, coupled with the poor specificity of the system, has resulted in a poor cancer detection rate and a steadily growing volume of hospital referrals. The system has been shown to have an adverse impact on the waiting times for routine colorectal referrals. In fact, only 24% of incident CRC cases were diagnosed through the TWW, and no evidence was found that CRC was diagnosed at an earlier stage. Jellema et al. evaluated the diagnostic accuracy of the TWW. The sensitivity and specificity for CRC detection were
Additionally, the diagnostic yield for CRC (OR = 2.41; 95%CI: 1.31-4.42) and detection of significant colonic lesions (OR = 1.88; 95%CI: 1.13-3.15) increased when colonoscopies were referred directly from primary care providers.

Several studies have been performed to develop predictive indexes for CRC detection in recent years. The aim was to establish objective criteria that are more accurate for CRC and to detect relevant findings, thus reducing the number of referrals to colonoscopy. Selvachandran et al developed one of the first predictive systems: The Weighted Numerical Score (WNS). The WNS is derived from the weighting of primary symptoms and symptom complexes and is automatically derived from a patient consultation questionnaire linked to a computerized record. In the validation study, the sensitivity of the WNS for CRC at a 40-point threshold reached 99%. In addition to having similar cancer detection rates as the TWW system, the specificity of the WNS cut-off of 70 was significantly better than that of the TWW system (82.7% vs 66.1%; P < 0.001). Thus, the WNS was subsequently validated, both internally and externally, showing similar detection rates with greater specificity. Unfortunately, it has only been validated for the detection of distal tumours and requires licensed software.

Adelstein et al published a predictive model based on symptoms collected using a validated questionnaire, demographic variables and medical history. On the basis of a range of symptoms (anaemia, rectal bleeding, abdominal pain and mucus passage to the rectum), age, sex, colonoscopy in the past 10 years, use of nonsteroidal anti-inflammatory drugs or aspirin, and history of irritable bowel syndrome, they obtained a predictive model with an area under the curve (AUC) of 0.83 for CRC detection. The Cancer Prediction in Exeter (CAPER) and the Bristol-Birmingham (BB) equation are two additional CRC scoring systems. The CAPER score is derived from a primary care case-control study and the BB equation from a large primary care dataset. Their discrimination characteristics were investigated in two datasets (BB and CAPER dataset) and its diagnostic accuracy for CRC detection was compared with the TWW guideline. Both multivariable symptom scoring systems performed significantly better than NICE referral guidelines: AUC of the BB equation: 0.83 (95%CI: 0.82-0.84) and 0.92 (95%CI: 0.91-0.94), respectively; AUC of the CAPER score: 0.79 (95%CI: 0.79-0.80) and 0.91 (95%CI: 0.89-0.93), respectively; and AUC of the TWW rule: 0.65 (95%CI: 0.64-0.66) and 0.75 (95%CI: 0.72-0.79), respectively.

Therefore, prioritization criteria based on symptoms and signs seem to have poor diagnostic accuracy for CRC, while predictive indexes that add demographic variables and/or analytical data worked better. This highlights the need to develop more objective tools to reduce CRC delay due to waiting lists.

**BIOMARKERS**

Currently, there are several biomarkers available for the diagnosis of CRC.
evaluation of symptomatic patients. They include blood and faecal tests, such as serum and faecal haemoglobin (FOBT), serum carcinoembryonic antigen and faecal calprotectin.

Although serum haemoglobin is not a biomarker, its association with the risk of CRC detection and other colorectal diseases is clearly described. As shown previously (Table 1 and Figure 1), iron deficiency anaemia is highly specific for CRC detection (92%), although it lacks sensitivity[22-24]. Other available serum biomarkers, such as carcinoembryonic antigen (CEA), have been evaluated. However, lack of specificity and sensitivity preclude the use of all existing serum markers for the early detection of CRC. CEA determination is limited to surveillance after CRC resection with a curative intent[79].

Faecal calprotectin has recently emerged as a candidate biomarker for intestinal inflammation with a potential clinical application as a diagnostic adjunct in IBD and other pathologies of the gastrointestinal tract[80-82]. Calprotectin levels have been found to be significantly elevated in patients with inflammatory and neoplastic conditions[80]. Despite this, the meta-analysis performed by von Roon et al[80], which included 7 studies with 2661 patients to evaluate CRC detection, did not show significant differences among patients with CRC and controls. Patients with colorectal neoplasia had non-significantly higher calprotectin levels (132.2 µg/g higher) compared with non-cancer controls (P = 0.18). The sensitivity and specificity of calprotectin for the diagnosis of CRC were 36% and 71%, respectively, with an AUC of 0.66.

Multiple studies have demonstrated that CRC screening with chemical FOBT in average-risk populations significantly reduces CRC mortality[83]. To date, no data are available regarding the effect of FIT on CRC mortality or incidence. However, several studies on diagnostic tests have compared chemical FOBT and FIT for the detection of CRC and advanced adenomas. These studies have shown that FIT is more sensitive and specific for the detection of CRC and advanced adenomas and is a cost-effective screening test[84]. Current CRC screening programs are based mainly on FIT. In contrast, the information available on the evaluation of symptomatic patients is scarce. In the meta-analysis published by Jellem et al[24], FIT had a 95% sensitivity and a 84% specificity for CRC detection with a 21% PPV and a 100% NPV (Table 1). However, the studies included in this meta-analysis mixed asymptomatic and symptomatic patients and were performed in secondary care settings. However, the authors concluded that FIT showed good diagnostic performance for CRC.

Four additional studies have recently evaluated the diagnostic accuracy of FIT for CRC detection in symptomatic patients[85,86-87]. In these studies, FIT at different thresholds (10 ng/mL and 20 ng/mL) had an adequate diagnostic accuracy for CRC detection. The ranges of sensitivity, specificity, PPV and NPV were 74.7%-100%, 77.4%-93.9%, 7.6%-53% and 97.8%-100%, respectively. Moreover, in our recently published article, we compared FIT (20 ng/mL cut-off point) with the NICE criteria[7]. Among 787 patients referred for colonoscopy, we detected 97 cases of CRC. FIT had a higher sensitivity (87.6%, 61.9%; P < 0.001) and specificity (77.4%, 42.7%; P < 0.001) for CRC detection than the NICE criteria. Moreover, while the NICE referral criteria was modified according to the CRC location (rectum 76.7%, distal colon 61.4%, proximal colon 43.5%; P = 0.01), FIT sensitivity was not modified by its location (rectum 90%, distal 75%, proximal 87%; P = 0.2)[85]. Finally, McDonald et al[85] also evaluated the diagnostic accuracy of FIT for the detection of significant colonic lesions (CRC, advanced adenoma, IBD) in symptomatic patients. They also exhibited good results (sensitivity, 57%; specificity, 99%; PPV, 62% and NPV, 81.6%). These results are concordant with the results obtained in our series (not published). We found that the sensitivity and specificity of FIT for the detection of significant colonic lesions were 60.2% and 82.4%, respectively, and PPV and NPV were 60.2% and 82.4%, respectively.

In summary, biomarkers appear to be a promising tool for the prioritization of CRC in symptomatic patients. Currently, FIT has demonstrated its accuracy as a prioritization tool alone, and its use should be increased. In the coming years, we should see the emergence of new biomarkers.

**CONCLUSION**

In conclusion, the value of symptoms as predictors of CRC or relevant colonic findings is poor. In the complexity of the cancer diagnosis, delays can occur in the different phases from the appearance of symptoms until final diagnosis (patient-related, physician-related and hospital-related factors). Understanding the factors that produce the delay is the first step to improving the diagnostic process and reducing the time interval from the first symptoms until diagnosis, improving CRC prognosis. The appropriateness criteria for colonoscopy can be a basis to control the quality of referrals, identifying unnecessary tests, but its value as a diagnostic tool is limited, especially in symptomatic patients. Several prioritization criteria and predictive indexes have been developed. All of them have insufficient sensitivity for CRC detection, so CRC cannot be ruled out in those patients who do not meet these criteria. Moreover, these criteria and indexes are nonspecific and are based mainly on the subjective evaluation of symptoms, thus yielding unnecessary colonoscopies. Finally, the use of biomarkers in symptomatic patients is promising. Adding available biomarkers, especially FIT, to risk classification scores and predictive indexes may increase both the sensitivity and specificity of CRC detection, thus reducing the number of patients referred for colonoscopy to evaluate symptoms and increasing the diagnostic yield of colonoscopy in this setting.
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