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Evidence-Based Series 24-1 Version 2

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers

The Colorectal Cancer Referral Expert Panel

An assessment conducted in March 2024 deferred the review of Evidence-Based Series (EBS) 24-1 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 24-1 Version 2 is comprised of 4 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/586

Section 1: Guideline Recommendations (ENDORSED)
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Tool

April 10, 2017

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original April 2012	June 2004 – August 2011	Full Report	Peer review publication Web publication	NA
Current Version 2 April, 2017	June 2009 - September 2015	New data found in Section 4: Document Review Summary and Tool	Updated CCO web publication	2012 recommendations **ENDORSED**

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Evidence-Based Series 24-1: Section 1- Guideline Recommendations

Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers: Guideline Recommendations

L. Del Giudice, E. Vella, A. Hey, W. Harris, M. Simunovic, C. Levitt, and the Colorectal Cancer Referral Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 24, 2012

These guideline recommendations have been ENDORSED in April 2017, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2009 and 2015 and for details on how this Clinical Practice Guideline was ENDORSED on page 102.

QUESTIONS

Overall Question

How should patients presenting to family physicians (FPs) and other primary care providers (PCPs) with signs and/or symptoms of colorectal cancer (CRC) be managed? The following questions are the factors considered in answering the overall question:

1. What signs, symptoms, and other clinical features that present in primary care are predictive of CRC?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of CRC?
3. What major, known risk factors increase the likelihood of CRC in patients presenting with signs and/or symptoms of CRC?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION

Adult patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients who present with alarming emergency symptoms and signs of hemodynamic instability, acute gastrointestinal hemorrhaging, acute intestinal obstructions, or unremitting abdominal pain. These patients should be immediately referred to emergency for assessment and treatment. In addition, this guideline does not address CRC screening for asymptomatic patients.

INTENDED USERS

This guideline is intended for FPs, general practitioners, emergency room physicians, other PCPs (nurse practitioners, registered nurses, and physician assistants), surgeons and gastroenterologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as 'FPs and other PCPs'. Along the diagnostic assessment pathway, FPs and other PCPs should apply the College of Physicians and Surgeons of Ontario's policy on Test Results Management to ensure that an appropriate response to test results is met (1). This guideline is also intended for policymakers to help ensure that resources are in place so that target wait times can be achieved. This guideline coincides with the introduction of colorectal cancer Diagnostic Assessment Programs (DAPS) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to improve patient access and outcomes, and are outlined in *Ontario Cancer Plan 2005-2011* and *Ontario Cancer Plan 2011-2014* (2).

Added in December 2019: Formal Cancer Care Ontario DAPs no longer exist in Ontario, but many hospitals provide ongoing multidisciplinary team approaches to diagnosing colorectal cancer.

RECOMMENDATIONS

Clinical Presentation
A focused history and physical examination should be performed if patients present with one or more of the following signs or symptoms: • Palpable rectal mass • Palpable abdominal mass • Anemia (especially iron-deficiency anemia) • Rectal bleeding • Change in bowel habits • Weight loss • Abdominal discomfort • Perianal symptoms

The focused history should determine the following details:
• Age and gender
• Rectal bleeding, and if yes,
  - Colour (dark versus bright red)
  - Location of blood relative to stool (mixed in with stool versus separate from stool, on the toilet paper)
• Change in bowel habit over recent months/years, and if yes,
  – Increased loose or watery stools or diarrhea
  – Increased constipation or difficulty passing stools
  – Feeling of incomplete emptying
  – Increased urgency
  – Incontinence of stools or soiling

- Weight loss
- Abdominal discomfort (pain, tenderness, bloating)
- Perianal symptoms such as prolapsed lump, pruritus, pain, hemorrhoids
- Symptoms of anemia [e.g., fatigue, weakness - refer to anemia guidelines (3,4)]
- If unexplained iron-deficiency anemia present, explore possible causes of blood loss or blood dyscrasia (3,4).
- Personal history of colorectal polyps or inflammatory bowel disease (IBD) or a first-degree family history of CRC and the age of onset

To supplement the history, a focused physical examination or investigations should include the following:

- Digital rectal examination (DRE)
- Abdominal examination. If palpable mass detected, order abdominal/pelvic imaging.
- Look for signs of anemia - refer to anemia guidelines (3,4)
- Weight (and comparison to previous weights if possible)
- Complete blood count (CBC), and if low mean cell or corpuscular volume (MCV) (i.e., microcytic anemia), may order ferritin

Referral

Qualifying Statement – Added to the Endorsement in April 2017:
The original 2012 guideline included a discussion of an option to test with the fecal occult blood test (FOBT) in a narrow set of circumstances. In the 2017 version, because of the possible negative impact of the 2012 recommendation regarding FOBT on the organized colorectal cancer screening program in Ontario, it was decided to remove all recommendations associated with FOBT from the guidance for referral, from the summary of key evidence, and from the accompanying algorithm.
Added in December 2019: *The statement above regarding the exclusion of FOBT from guidance for referral also applies to the fecal immunochemical test (FIT).*

Referral and wait time recommendations for the following indications are based on evidence of the relative predictability for CRC of single or combined signs, symptoms, or diagnostic investigations (5). The referral wait times also align with the recommendations developed by the Canadian Association of Gastroenterology (6). In many jurisdictions, organized Diagnostic Assessment Programs (DAPs) with centralized referral access may facilitate timely tests and specialist appointments.

1. URGENT REFERRAL
   Referring physicians should send a referral to a CRC DAP or a specialist competent in endoscopy within 24 hours, expect a consultation within 2 weeks, and expect a definitive diagnostic workup to be completed within 4 weeks of referral, if a patient has at least one of the following:
   - Palpable rectal mass suspicious for CRC
   - Abnormal abdominal imaging result suspicious for CRC

2. SEMI-URGENT REFERRAL
   Referring physicians should send a referral to a CRC DAP or a specialist competent in endoscopy within 24 hours, expect a consultation within 4 weeks, and expect a definitive diagnostic work up to be completed within 8 weeks of referral, if a patient has at least one of the following:
   - Unexplained rectal bleeding in patients with at least one of the following characteristics or combinations of symptoms:
     - Dark rectal bleeding
     - Rectal bleeding mixed with stool
     - Rectal bleeding in the absence of perianal symptoms
     - Rectal bleeding and change in bowel habits
     - Rectal bleeding and weight loss
   - Unexplained iron-deficiency anemia (hemoglobin of ≤110 g/L for males or ≤100 g/L for non-menstruating females and iron below normal range)

Referring physicians should include information that may increase the likelihood of CRC in the consultation request:
- Patients aged 60 years and older
- Male patients
- The presence of two or more signs or symptoms
- Patients with a personal history of colorectal polyps or IBD or a first-degree family history of CRC

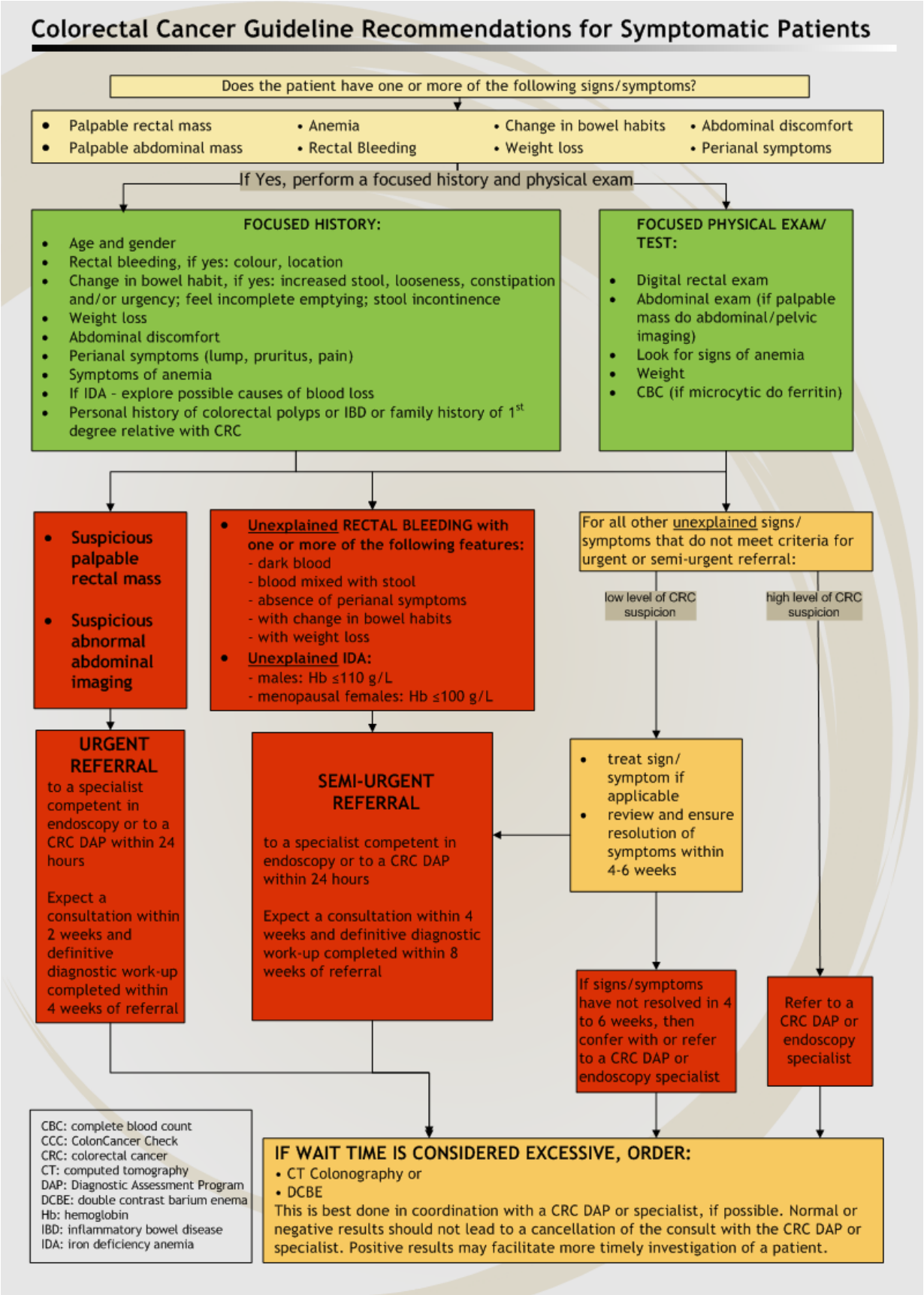
3. If the unexplained signs or symptoms of patients do not meet the criteria for referral but, based on clinical judgement, there remains a:
   - high level of suspicion of CRC, then refer to a CRC DAP or a specialist competent in endoscopy
   - low level of suspicion of CRC, then treat the sign and/or symptom if applicable. Review and ensure resolution of symptoms within four to six weeks. If signs and/or symptoms have not resolved in four to six weeks, then confer with or refer to a CRC DAP or specialist competent in endoscopy.

In situations where wait times for specialists to perform colonoscopy are considered excessive, referring physicians may order (depending on locally available resources):
- Computed tomographic (CT) colonography
- Double-contrast barium enema (DCBE)

This is best done in coordination with the CRC DAP or specialist, if possible. Normal or negative results should not lead to a cancellation of the consult with the CRC DAP or specialist. Positive results may facilitate more timely investigation of a patient.

Recommendations to Reduce Diagnostic Delay
• Information regarding the signs and symptoms of CRC, how to obtain a proper detailed history, physical examination, appropriate investigations, and referral of patients presenting with suspicious signs and symptoms should be widely disseminated to FPs and other PCPs using various knowledge translation strategies. • During the periodic health examination, FPs and other PCPs should ask adult patients about rectal bleeding, changes in bowel habits, and unintentional weight loss. • While discussing colorectal cancer screening with patients, FPs and other PCPs should ask about family history for CRC and the signs and symptoms predictive of CRC. • FPs and other PCPs should investigate unexplained anemia, especially iron-deficiency anemia. Refer to anemia guidelines (3,4) • For signs and symptoms that may not have prompted initial referral, FPs and other PCPs should reassess and further workup if signs/symptoms do not resolve. • FPs and other PCPs should consider training staff regarding triaging of patients calling with signs and/or symptoms suggestive of CRC to expedite initial appointments. • CRC DAPs and specialists competent in endoscopy should develop triage protocols to avoid delays in the diagnosis of CRC in patients with suspicious signs and/or symptoms. • Sustainable public education about the signs and symptoms of CRC, the importance of early detection and management, as well as common fears and concerns that may delay referral, should be developed and implemented. • Special efforts should be made to reduce delays in presentation often observed among women, single patients, younger patients, visible minorities, and patients with co-morbidities, decreased social support, lower levels of education, or a rural residence.

ALGORITHM


Colorectal Cancer Guideline Recommendations for Symptomatic Patients
Does the patient have one or more of the following signs/symptoms?
• Palpable rectal mass
• Palpable abdominal mass
• Anemia
• Rectal Bleeding
• Change in bowel habits
• Weight loss
• Abdominal discomfort
• Perianal symptoms
If Yes, perform a focused history and physical exam
FOCUSED HISTORY:
• Age and gender
• Rectal bleeding, if yes: colour, location
• Change in bowel habit, if yes: increased stool, looseness, constipation and/or urgency; feel incomplete emptying; stool incontinence
• Weight loss
• Abdominal discomfort
• Perianal symptoms (lump, pruritus, pain)
• Symptoms of anemia
• If IDA - explore possible causes of blood loss
• Personal history of colorectal polyps or IBD or family history of 1st degree relative with CRC
FOCUSED PHYSICAL EXAM/ TEST:
• Digital rectal exam
• Abdominal exam (if palpable mass do abdominal/pelvic imaging)
• Look for signs of anemia
• Weight
• CBC (if microcytic do ferritin)
• Suspicious palpable rectal mass
• Suspicious abnormal abdominal imaging
• Unexplained RECTAL BLEEDING with one or more of the following features:
- dark blood
- blood mixed with stool
- absence of perianal symptoms
- with change in bowel habits
- with weight loss
• Unexplained IDA:
- males: Hb ≤110 g/L
- menopausal females: Hb ≤100 g/L
For all other unexplained signs/ symptoms that do not meet criteria for urgent or semi-urgent referral:
low level of CRC suspicion
high level of CRC suspicion
URGENT REFERRAL
to a specialist competent in endoscopy or to a CRC DAP within 24 hours
Expect a consultation within 2 weeks and definitive diagnostic work-up completed within 4 weeks of referral
SEMI-URGENT REFERRAL
to a specialist competent in endoscopy or to a CRC DAP within 24 hours
Expect a consultation within 4 weeks and definitive diagnostic work-up completed within 8 weeks of referral
• treat sign/ symptom if applicable
• review and ensure resolution of symptoms within 4-6 weeks
If signs/symptoms have not resolved in 4 to 6 weeks, then confer with or refer to a CRC DAP or endoscopy specialist
Refer to a CRC DAP or endoscopy specialist
CBC: complete blood count
CCC: ColonCancer Check
CRC: colorectal cancer
CT: computed tomography
DAP: Diagnostic Assessment Program
DCBE: double contrast barium enema
Hb: hemoglobin
IBD: inflammatory bowel disease
IDA: iron deficiency anemia
IF WAIT TIME IS CONSIDERED EXCESSIVE, ORDER:
• CT Colonography or
• DCBE
This is best done in coordination with a CRC DAP or specialist, if possible. Normal or negative results should not lead to a cancellation of the consult with the CRC DAP or specialist. Positive results may facilitate more timely investigation of a patient.

KEY EVIDENCE

Clinical Presentation

The Colorectal Cancer Referral Working Group believe that the signs and symptoms listed under clinical presentation should alert FPs and other PCPs about the suspicion of CRC. The presenting signs or symptoms for which urgent or semi-urgent referral was recommended met one of two criteria: the sign or symptom presented in at least 5% of patients with confirmed CRC, or the sign or symptom was a statistically significant predictor of CRC. The exception to this is perianal symptoms. The absence of perianal symptoms with rectal bleeding strengthens the positive predictive value (PPV) for CRC rather than the presence of perianal symptoms. The studies included in calculating median PPVs or that contained multiple regression analyses can be found in Section 2 of this report.

For the signs and symptoms of anemia as well as the questions to ask patients presenting with unexplained anemia, the Working Group decided that primary care physicians could refer to reference documents such as the *Anemia Guidelines for Primary Care* developed by Medication Use Management Services Guidelines Clearinghouse and/or the *Guidelines for the Management of Iron deficiency Anaemia* by the British Society of Gastroenterology (3,4).

Risk factors

In a patient presenting with rectal bleeding, anemia or change in bowel habits, there is evidence to suggest that increasing age and male gender may increase the predictability of suspicion for CRC (described below under Referral).

Meta-analyses by Olde Bekkink et al and Jellema et al found high specificity but low sensitivity for a family history of CRC in symptomatic patients (9,10). In addition, Jellema et al reported a pooled PPV of 6% for a family history of CRC in symptomatic patients (9). There is well-established evidence that patients with a personal history of colorectal polyps or IBD are at increased risk of CRC (11). Based on the consensus, the Working Group decided that for these patients who are part of a surveillance program and present with interim signs or symptoms of CRC, early re-referral to specialists is recommended.

Investigations

There was a paucity of studies examining the diagnostic accuracy investigations for patients presenting with signs and/or symptoms of CRC. The physical examination manoeuvres that were included were based on consensus. They are simple, can be easily performed in primary care, and can provide valuable information leading to expedited referral. Proctoscopy was not recommended as a standard of care due to a lack of evidence for its use, a lack of widespread availability, and a low rate of use in primary care. However, based on consensus, it may still be used at the discretion of the clinician.

The following diagnostic investigations are recommended by the Working Group for completion of the assessment: CBC and imaging for palpable abdominal masses. The results of these tests should be made available to the specialists. Although there were very few studies examining the diagnostic accuracy of a CBC for predicting CRC in symptomatic patients, there was consensus that this should be ordered to assist in the evaluation of whether anemia, and especially iron-deficiency anemia, is present. A ferritin should be ordered if IDA is suspected. It is common practice to image abdominal masses found during a physical examination. Imaging may help to determine whether the mass is intra-colonic or extra-colonic and direct the workup of the mass, as well as indicate appropriate specialty referral.

Because there were very few studies examining the diagnostic accuracy of carcinoembryonic antigen (CEA), erythrocyte sedimentation rate (ESR), and other blood tests for predicting CRC in symptomatic patients, they were not recommended.

Referral

The Working Group chose to include signs or symptoms with median PPVs greater than 10%, identified in studies in Section 2 of this report, as indicators for referral. For triaging purposes in patients who are being referred semi-urgently, the following combinations of clinical features have been found to increase the index of suspicion for CRC and are described in Section 2 of this report:

- Increasing age (most studies used a cutoff of greater than or equal to 60 years) and rectal bleeding or change in bowel habits or anemia (especially iron-deficiency anemia)
- Male patients with rectal bleeding or change in bowel habits or anemia (especially iron-deficiency anemia)
- A combination of signs or symptoms

For signs or symptoms that did not lead to referral, the Working Group chose to rely on clinical judgement to decide whether there was a high level or low level of suspicion for CRC. The Working Group decided that if a clinician has a low level of suspicion, signs and symptoms should be treated and resolution in four to six weeks should be ensured. This time frame was chosen based on the clinical experience of the Working Group and to be consistent with the NICE and NZGG guidelines that recommend referral when some of these symptoms (e.g., rectal bleeding, change in bowel habits) persist for at least six weeks (7,8).

If the time to referral exceeds the recommended wait times or is considered excessive, the Working Group recommended that the referring physician may consider ordering a CT colonography or DCBE, depending on locally available resources. This would ensure that as much information as possible would be made available to the specialist during the consultation. There is some evidence to suggest that CT colonography or DCBE may have good diagnostic properties in symptomatic patients. The sensitivities and/or specificities were over 83% when CT colonography or DCBE were compared to colonoscopy alone (12-24). Flexible sigmoidoscopy (FS) also showed good sensitivity for detecting CRC, especially when combined with DCBE (13,16,22,25). However, the Working Group preferred that the entire colon be visualized. There were few studies examining the diagnostic accuracy of abdominal CT or abdominal or pelvic ultrasound among symptomatic patients; however, as described above, they may be helpful in differentiating abdominal/pelvic masses.

Factors Contributing to Diagnostic Delay

Although the evidence suggests that delay in referral does not have an impact on patient survival, the Working Group believed it was important to improve wait times with the intention of decreasing patient anxiety. Evidence from prospective and retrospective studies described in Section 2 of this report suggest that the following may delay the diagnosis of CRC:

- FP and other PCP-related delays (7,8,26-28)
  - failure to recognize signs and symptoms were suggestive of CRC
  - failure to investigate iron-deficiency anemia
  - failure to perform DRE
  - initial referral to a specialist without a gastrointestinal interest
  - receiving inaccurate or inadequate tests
  - frequent visits following an inconclusive first visit
  - patients with colon cancer referred less quickly than patients with rectal cancer
  - younger patients
  - gender (females had longer delays than males)
  - visible minorities

- Patient-related delays (7,8,26,27,29)

- patient's lack of appreciation regarding the association of symptoms with CRC
- fear that tests might be unpleasant or embarrassing
- uncomfortable with or embarrassed about symptoms, including pain, nausea, and vomiting
- decreased social support
- presence of co-morbidity
- rural residency
- lower education level
- single/separated/divorced
- female colon cancer patients had longer delays than male
- male rectal cancer patients had longer delays than females

FUTURE RESEARCH

Further studies should be designed to determine which educational initiatives would be best at decreasing practitioner or patient-related delay. Also, more studies to determine the diagnostic performance of signs and symptoms for CRC are needed in the primary care setting.

Updating

This document will be reviewed in three years to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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Contact Information

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Evidence-Based Series 24-1: Section 2 - Evidentiary Base

Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers: Evidentiary Base

L. Del Giudice, E. Vella, A. Hey, W. Harris, M. Simunovic, C. Levitt, and the Colorectal Cancer Referral Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 24, 2012

The 2012 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Below is the original summary of evidence from 2012. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2009 and 2015 and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTIONS

Overall Question

How should patients presenting to family physicians (FPs) and other primary care providers (PCPs) with signs and/or symptoms of colorectal cancer (CRC) be managed? The following questions are the factors considered in answering the overall question:

1. What signs, symptoms, and other clinical features that present in primary care are predictive of CRC?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of CRC?
3. What major, known risk factors increase the likelihood of CRC in patients presenting with signs and/or symptoms of CRC?

4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

INTRODUCTION

CRC is one of the most common types of cancer for both men and women in Ontario, with an incidence of 7494 cases in 2006 (1). The number of cases has increased over the past three decades, mostly as a result of population aging (1). CRC is also the second leading cause of cancer-related deaths in Ontario, with 3026 deaths in 2006 (1). However, when CRC is detected early, there is a 90% chance that it can be cured. In recent years, half the reported CRC cases were diagnosed at an early stage (I or II), and half were diagnosed at later stages (III or IV) (1).

In an attempt to improve the rate of early detection of CRC in Ontario, a population-based screening program, ColonCancerCheck, has recently been implemented (2). However, although CRC screening rates are increasing, they are currently still low (30% in 2007-2008) (1). As a result, many patients with CRC will present to their FPs and other PCPs unscreened and with signs or symptoms of CRC. To date, there are no evidence-based guidelines that can assist FPs and other PCPs in Ontario to identify CRC and initiate the management of these patients. The CCO Provincial Primary Care and Cancer Network (PPCCN) has collaborated with the PEBC to develop guidelines for patients who present with signs and symptoms that could be suspicious of CRC. The New Zealand Guidelines Group (NZGG) 2009 guideline *Suspected Cancer in Primary Care: Guidelines for Investigation, Referral and Reducing Ethnic Disparities* and the National Institute for Health and Clinical Excellence (NICE) 2005 guideline *Referral Guidelines for Suspected Cancer in Adults and Children* were chosen as baseline documents for the development of this systematic review (3,4). As well, the Ontario recommendations were designed to complement the Ontario CRC Screening Program (2). The aim of this guideline is to assist FPs and other PCPs to recognize features that should raise their suspicions about the presence of CRC in their patients and ultimately lead to more timely and appropriate referrals for them.

METHODS

The evidence-based series guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (5). A priori, the Colorectal Cancer Referral Working Group chose the evidence-based NZGG 2009 and NICE 2005 documents as a foundation, because they were considered to be of high quality, comprehensive, recent in publication, and relevant to this topic (3,4). In addition, the Working Group chose to use the modified research questions from the NZGG guideline (4). The Working Group updated the literature searches of the NZGG and the NICE systematic reviews (3,4). Evidence was selected by one methodologist and reviewed by the Working Group and Colorectal Cancer Referral Expert Panel (Appendix 1).

This systematic-review update is a convenient and up-to-date source of the best available evidence on primary care referral for suspected CRC. The body of evidence in this review is primarily comprised of guidelines, meta-analyses, and prospective and retrospective studies. This evidence forms the basis of the recommendations developed by the Working Group and approved by the Expert Panel. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

To determine whether there were other higher quality guidelines compared to the NICE or NZGG reports or guidelines with more recent systematic reviews, or what other agencies were recommending, a targeted environmental scan of international guideline developers and key organizations was conducted (July 3, 2009) for documents about primary care referral for suspected CRC. Appendix 2 provides a list of the organizations that were examined.

As a result of this search for other guidelines, the Working Group considered the NICE 2005 and NZGG 2009 guidelines to be of the highest quality and updated their literature search strategies (3,4). The search strategies from NZGG 2009 and NICE 2005 were kindly provided to us for this systematic review (3,4).

For signs and symptoms, an updated search, since the NICE publication, of MEDLINE (Ovid, June 2004- June 2009) and EMBASE (Ovid, 2004-2009 week 23) was performed using the combined NZGG and NICE literature search strategies (3,4). For diagnostic tests, the NZGG search strategies were modified to reflect tests that primary care providers in Ontario can perform or order such as a complete blood count (CBC), fecal occult blood testing (FOBT), barium enema, anoscopy, and ultrasound, and included terms suggested by the Working Group such as serum iron, iron blood level, virtual colonography, and virtual colonoscopy (4). An updated search, since the NICE publication, of MEDLINE (Ovid, June 2004- June 2009) and EMBASE (Ovid, 2004-2009 week 24) was then performed.

For the research question about delay, an updated search, since the NZGG publication, of MEDLINE (Ovid, Sept 2007-June 2009) and EMBASE (Ovid, 2007-2009 week 25) using the NZGG search strategies for delay for colorectal cancer was performed (4). For risk factors, an updated search, since the NICE publication, of MEDLINE (Ovid, June 2004- June 2009) and EMBASE (Ovid, 2004-2009 week 23), using the NICE search strategies for systematic reviews for CRC was performed (3). The search strategies can be found in Appendix 3. A literature search update of all strategies for studies available to August 2011 was conducted.

Study Selection Criteria

Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG or NICE guidelines, and included recommendations not found or different from those in either the NICE or NZGG guidelines (3,4).

Studies, found from reference lists, that were published before the NICE or NZGG guidelines but were not included in their reports were included in this systematic review if they addressed any of the research questions and met the inclusion criteria (3,4).

This report focuses on adult patients presenting to primary care with signs or symptoms of CRC. For the clinical question regarding the predictive characteristics of signs or symptoms, all comparative studies of symptom recognition and/or identification for CRC were included. Studies that reported only the main signs or symptoms for each patient, ignoring the presence of additional signs or symptoms, were excluded. Studies where CRC was found in only one patient were also excluded. Studies conducted in secondary care settings were included if they provided predictive information about signs and/or symptoms for suspected CRC; however, they may not have been taken as strongly into consideration as were primary care data when developing the recommendations. Screening studies were excluded because they include asymptomatic patients.

All diagnostic studies were sought in which adult symptomatic primary care patients underwent one or more investigations that included computed tomographic (CT) colonography, barium enema, sigmoidoscopy, ultrasound, CT scan, digital rectal examination (DRE), proctoscopy, rectoscopy, anoscopy, fecal occult blood tests (FOBTs), or complete blood counts (CBC). Studies involving investigations for carcinoembryonic antigen (CEA), C-reactive protein, erythrocyte sedimentation rate (ESR), ferritin, or serum iron were also searched. Studies conducted in secondary care settings were included if they provided diagnostic information for

suspected CRC for the specified investigations; however, they may not have been considered as strongly as the primary care data when developing the recommendations. Screening studies were excluded.

For the clinical questions concerning risk factors and delay, a search for practice guidelines, systematic reviews with meta-analyses, and systematic reviews without meta-analyses was performed. If these articles did not definitively answer the particular clinical question, searches for randomized phase III trials and randomized phase II trials, followed by comparative studies, were performed. If the information from systematic reviews definitely answered the question(s), articles from the time of publication of the systematic review and onwards were searched. To develop recommendations with feasible wait times for Ontario, articles assessing wait times in Canada were also included, regardless of study design.

Non-English publications were not eligible due to the lack of translation funding. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Synthesizing and Presenting the Evidence

Data were not pooled because considerable heterogeneity existed between studies for the selection of the patient population, diagnostic tests used to confirm CRC, and prevalence of CRC across studies. Formulas used to calculate the confidence intervals (CIs) of sensitivity, specificity, positive-predictive values (PPV), and negative-predictive values (NPV) were found in Lipsey and Wilson 2001, for likelihood ratios in Katz et al 1978, and for odds ratios (ORs) in Deeks 2001 (6-8). Due to the heterogeneity between studies, median PPVs were calculated only if PPVs were reported in at least four studies for any given sign or symptom. PPVs from each included study were used to calculate median PPVs for a given sign or symptom. (9)

Quality Appraisal of Evidence-Based Guidelines and Systematic Reviews

The Appraisal of Guidelines Research and Evaluation (AGREE II) tool was used by three independent methodologists to evaluate the quality of included evidence-based guidelines (10,11). Only clinical practice guidelines where the guideline objective was specifically described and the document included a review of the evidence were evaluated using the AGREE II tool. Systematic reviews and meta-analyses were assessed for quality using the 'assessment of multiple systematic reviews' tool, the AMSTAR tool (12).

RESULTS

Literature Search Results

Of 21,006 articles identified in the literature search done since the NICE and NZGG guidelines searches, 121 were deemed relevant for a full-article review (3,4). For the clinical question pertaining to the diagnostic accuracy of signs and symptoms in predicting CRC, a post hoc decision was made to focus on PPVs. Since PPVs are affected by the prevalence in the population, PPVs from primary studies conducted in the secondary care setting were excluded. Other excluded studies included those that did provide PPVs or PPVs could not be calculated, or where the main outcome was organic disease or polyps and not CRC. Therefore, 29 articles since the NICE and NZGG systematic reviews met the revised inclusion criteria and were retained (13-41). Nineteen articles were found in the updated literature search (42-61), 31 articles were found in reference lists of included articles (62-92), and one guideline was found during the environmental scan (9). In total, in addition to the NICE and NZGG guidelines, four guidelines, nine meta-analyses, two systematic reviews, and 66 primary studies were included (3,4,9,13-92). Table 1 summarizes the included articles for each research question.

Table 1. Summary of literature used for each research question.

Research Question	Guideline	Meta-analysis	Systematic review	RCT	Prospective studies	Retrospective studies	Case-control studies
Signs / symptoms	2*	6**	1	0	18	5	3
Tests	2*	2**	0	1	18	10	1
Risk factors	2*	2**	0	0	3	1	0
Delay	3*	2	1	0	5	12	0

Abbreviation: RCT = randomized controlled trial.

* 2 guidelines for each research question were from NICE and NZGG (3,4)

** 2 meta-analyses for signs/symptoms and risk factors were from Jellema et al (47) and Olde Bekkink et al (50); Jellema et al (47) was also included in the tests section.

Study Design and Quality

Guidelines

The NICE and NZGG guidelines were evaluated using the AGREE II Tool as described in the Methods section (Table 2) (3,4). Although the overall quality of these recent guidelines was rated as high, the Working Group decided the recommendations needed to be modified to reflect the availability of resources among Ontario FPs and other PCPs and to align them with the Ontario Colorectal Screening Program (2). However, the NICE and NZGG clinical questions and recommendations were used as a framework in the development of this guideline. As well, the evidentiary base of the NICE and NZGG guidelines were used to formulate new recommendations.

Two other guidelines had lower overall AGREE II scores (Table 2). One guideline by the Association of Coloproctology of Great Britain and Ireland (2007) was based on a literature review and consensus that were not described in detail (9). That guideline was not used as a basis for the development of this guideline, but the reference lists were searched for additional articles. A consensus guideline by the Canadian Association of Gastroenterology provided recommendations for wait times in Canada (31). Its lower overall score was due to the lack of literature in this area, resulting in the recommendations being developed through consensus. The target wait times were used as a framework to develop the recommendations in this guideline.

Table 2. Results of AGREE Tool quality rating of evidence-based guidelines.

Guideline	AGREE Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2005 (3)	96.3	88.9	77.8	87.0	81.9	27.8
NZGG 2009 (4)	92.3	94.4	59.2	88.9	44.4	72.2
Irish 2007 (9)	81.5	50	48.6	92.6	8.3	0
Canadian (Paterson 2006) (31)	79.6	74.1	58.3	96.3	8.3	83.3

Abbreviations: NICE = National Institute for Health and Clinical Excellence; NZGG = New Zealand's Guideline Group.

Two guidelines were not evaluated by the AGREE II Tool. A guideline developed through consensus by the British Society of Gastroenterology (2005) provided recommendations for the management of iron-deficiency anemia (IDA) and did not include a literature search (62). In addition, the consensus process was not described in detail. The other report, by Lee and

Laberge (2005), provided a diagnostic algorithm for the investigation of gastrointestinal bleeding (26). Although it did contain a narrative review of the literature, it was not clear whether the report was intended to be a clinical practice guideline.

Reviews

There were eleven systematic reviews found in the literature since the publication of the NICE and NZGG guidelines (3,4,18,22,28,32,33,42,44,47,48,50,54). One systematic review that investigated the diagnostic accuracy of signs or symptoms for CRC had a similar research question but included studies with asymptomatic patients and included studies where only one symptom was reported per patient (42). Since their inclusion criteria were different from this review, only the reference list was searched for additional articles. Table 3 shows how the ten remaining systematic reviews and meta-analyses scored on each of the 11 AMSTAR items. Six of the systematic reviews, five with meta-analyses, investigated the diagnostic accuracy of symptoms or signs for CRC (18,44,47,48,50,54). The five reviews with meta-analyses had high overall scores. Unlike this review, three of these reviews required the construction of two-by-two tables from the data (18,47,50) and one included signs or symptoms with PPVs greater than or equal to five percent (54). The systematic review without meta-analysis by John et al 2010 scored lower because the characteristics of included studies were not provided, and although the quality of each study was scored, the results for each study were not reported (48). Therefore, only the reference list for this article was searched for additional studies. Three other systematic reviews, two with meta-analyses, examined the factors associated with delay or the impact of delay on survival, and also had high overall AMSTAR scores (28,32,33). One meta-analysis by Koo (2006) investigating the diagnostic accuracy of minimal-preparation CT did not include a systematic review and, therefore, was scored lower (22).

Table 3. Evaluation of included publications using AMSTAR.

ITEM	Astin et al. 2011 (44)	Ford et al. 2008 (18)	Jellema et al. 2010 (47)	John et al. 2010 (48)	Koo et al. 2006 (22)	Mitchell et al. 2008 (28)	Olde Bekkink et al. 2010 (50)	Ramos et al. 2007 (32)	Ramos et al. 2008 (33)	Shapley 2010 (54)
1. Was an 'a priori' design provided?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	N	N	Y	Y	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
5. Was a list of studies (included and excluded) provided?	N	Y	Y	Y	N	Y	Y	N	N	N
6. Were the characteristics of the included studies provided?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	N	N	Y	Y	Y	Y	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	Y	NA	Y	NA	Y	Y	Y	Y
10. Was the likelihood of publication bias assessed?	N	N	Y	N	N	N	N	Y	Y	N
11. Was the conflict of interest stated?	N	N	N	N	N	N	N	N	N	N
TOTAL AMSTAR POINTS	8	9	10	5	3	7	8	9	9	8

Abbreviations: N = no; Y = yes; NA = Not applicable.

Primary Studies

The primary studies identified in the literature search, reference lists, and environmental scan included one randomized controlled trial (91); 35 prospective studies (14,16,17,21,23-25,27,34,35,37,45,49,58,61,64,65,68-71,73-75,77,79,80,82,85-90,92); 27 retrospective studies (13,15,19,29,36,38-41,43,46,51-53,55-57,59,60,63,66,67,76,78,81,83,84); and three case-control studies (20,30,72). The randomized controlled trial addressed the second research question, was not blinded, and was not performed in a primary care setting (91). Based on the Cochrane Collaboration method for assessing the methodological quality of diagnostic studies, using a modified QUADAS tool, several factors affected the quality of the included prospective, retrospective, and case-control studies (93). The details of these factors can be found in the evidence tables below. Some of these studies selected patients with specific signs or symptoms such as rectal bleeding and, therefore, may not be representative of the primary care population. Some studies did not recruit consecutive patients or were not blinded to the patients' diagnoses. There were also studies that did not adequately explain the missing or uninterpretable data or the reasons for patient withdrawals. In addition, the gold standard of colonoscopy for detecting CRC was not always used.

Outcomes

1. **What signs, symptoms and other clinical features that present in primary care are predictive of CRC?**

To facilitate relative comparisons between clinical features with screen-positive FOBTs, the evidence summaries below report PPVs. PPV is the probability that the disease is truly present when the test is positive. The majority of studies reported PPVs or the PPV could be easily calculated. The estimated PPV for the detection of CRC, using Hema Screen, the FOBT used in the Ontario ColonCancerCheck screening program, of single (one-time) testing in asymptomatic patients was 10.9% (94). The combined median PPV for all guaiac FOBTs evaluated in a recent review was 5.7% (94). Therefore, PPVs in symptomatic patients greater than 5% and 10% are specifically highlighted in the summaries that follow. Since the focus was on PPVs, and PPVs are affected by the prevalence of the disease in the population, we only included PPVs from studies performed in primary care populations, although we did report the findings from two meta-analyses (18,47) that included secondary care studies, because their results focused on primary care referral. Jellema et al included secondary care studies only if the prevalence of CRC was less than 15%, which was the highest prevalence reported in the primary care studies (47). Two studies that were considered primary care in the Ford et al (2008) meta-analysis were categorized as secondary care studies in the Jellema et al meta-analysis (18,47). Based on the opinion of our Working Group, we have included these studies as primary care studies (82,92). Furthermore, we have included the studies conducted in the United Kingdom (UK) two-week referral clinics as primary care studies, because they were at the interface between primary and secondary care (13,61,67,71). These studies have been noted in the tables and appendices. The meta-analysis by Olde Bekkink et al (2010) included studies only from primary care, but all the studies selected for patients with rectal bleeding (50).

The PPVs of signs or symptoms and results from regression analyses can be found in the evidence tables (Appendices 4-14). Other pooled diagnostic parameters such as sensitivity, specificity, and positive-likelihood ratios are reported from the meta-analyses (Appendix 15). Study characteristics are provided in Table 4 and calculated median PPVs in Table 5. Studies were from the updated literature search done since the NZGG and NICE reports and reference lists and studies found in the NICE and NZGG reports. Since NICE and NZGG did not focus on PPVs and organized the data within the context of each study rather than each symptom or sign, the data in this review may not be easily compared to the data in these original reviews.

Table 4. Study characteristics for clinical questions about signs, symptoms or risk factors of colorectal cancer.

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
Astin 2011 (44)	Meta-analysis, UK, primary care	23 studies, 81,464 patients	0.4%-23.2%	various	various	various	various	various
Barwick 2004 (13)	Retrospective between January and August 2001, UK, Primary care (2WW)	144	14 (10)	various including barium enema, FS, ultrasound, colonoscopy	unclear	no	unclear	yes
Bat 1992 (65)	Prospective, Israel, primary care	101 ≥80 yrs with rectal bleeding	29 (29)	all colonoscopy	unclear	no	no	no
Chohan 2005 (67)	Retrospective over 18-month period, UK, Primary care 2WW referral	462	64 (13.8)	unclear, but included histopathology	yes	no	yes	yes
du Toit 2006 (69)	Prospective, UK, Primary care	265 Age ≥45 yrs, with rectal bleeding	15 (5.7)	mostly sigmoidoscopy with barium enema, FS, or colonoscopy; f/u 10 yrs 3 mths	yes	no	no	yes
Ellis 2005 (17)	Prospective, UK, primary care	319 with rectal bleeding	11 (3.4)	FS and barium enema or colonoscopy; f/u 18 mths	yes	unclear	yes	yes
Fijten 1995 (70)	Prospective from September 1988 to April 1990, Netherlands, primary care	269 with rectal bleeding	9 (3)	endoscopy, radiography, sigmoidoscopy, proctoscopy, sonography; f/u at least 1 yr	yes	yes	unclear	yes
Flashman 2004 (71)	Prospective over 1-yr period, UK, primary or secondary 2WW referral	695	65 (9) with bowel cancer	NR	yes	no	yes	yes
Ford 2008 (18)	Meta-analysis, Canada, primary and secondary care	15 prospective studies included	6% (5% to 8%)	colonoscopy, barium enema, CT colography, FS or any combination of the four	various	various	various	various
Hamilton 2008 (20)	Case control, UK, primary care records	3183 cases, 10,514 controls	3183	Electronic records, Hb taken in year before diagnosis	no	unclear	yes	unclear

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
Hamilton 2005 (72)	Case control, UK, Primary care records	349 cases, 1744 controls	349	Cancer registry	no	Yes to case/ control status	yes	yes
Heintz 2005 (21)	Prospective over 1-yr period, Germany, Primary care	422 with first sign of rectal bleeding	17 (4.0)	colonoscopies (n=195), rectoscopies (n=29), sigmoidoscopies (n=26)	no	yes	yes	yes
Helfand 1997 (73)	Prospective, USA, Primary care	201 with rectal bleeding	13 (6.5)	all sigmoidoscopy and barium enema, f/u 6-12 mths	no	no	yes	yes
Jellema 2010 (47)	Meta-analysis, Netherlands, Primary and secondary care	47 studies included	3%-15%	various	various	various	various	various
Jones 2007 (76)	Retrospective from January 1994 to December 2000, UK, Primary care records	7523 men, 7766 women with rectal bleeding	184 (2.4) men, 154 (2.0) women	NR from research database	no	no	yes	yes
Lawrenson 2005 (24)	Prospective, UK, Primary care records	2,793,468 (age 40-89 yr)	9143 (0.3% CRC after at least 1-yr f/u)	Medical database (symptoms included after 1-yr f/u)	yes	no	no	yes
Mant 1989 (77)	Prospective over 11 months, Australia, Primary care	145 Age >40 yr with rectal bleeding	16 (11)	mainly colonoscopy, some FS and air contrast barium enema; histopathology	yes	no	unclear	yes
Metcalf 1996 (90)	Prospective, UK, Primary care	99 Age >40 yrs with rectal bleeding	8 (8)	all colonoscopy, histopathology	yes	no	yes	yes
Muris 1993 (79)	Prospective over 15-month period, Netherlands, Primary care	578 with abdominal pain	3 (0.5)	X-ray, sonogram, endoscopy; f/u 15 mths	yes	unclear	no	yes
Norrelund 1996 (80)	Prospective, study 1: 1989-1991, study 2: 1991-1992, Denmark, primary care	study 1 = 208, study 2 = 209; all with rectal bleeding	study 1 = 32(15%), study 2 = 22(11%); excluded from analysis: if current bleeding similar to	Possibly barium enema/colonos-copy; microscopically verified; f/u study 1: 32-57 mths, study 2: 22-36 mths	yes	unclear	no	yes

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
			previous episodes					
Olde Bekkink 2010 (50)	Meta-analysis, Ireland, Scotland, Netherlands, Primary care	8 prospective studies, patients with rectal bleeding	7.0%	various	various	various	various	various
Panzuto 2003 (82)	Prospective over 8-week period, Italy, Primary care	280 exclude previous CRC diagnosis, recent large bowel examination	41 (14.6)	all colonoscopy or barium enema	yes	no	yes	yes
Park 2009 (30)	Nested case control, UK, primary care	159 cases and 771 controls	159	National cancer registry, avg 12-yr f/u	no	unclear	unclear	yes
Parker 2007 (83)	Retrospective April 1998 to March 2003, UK, primary care records	29,007 Age ≥25 yrs with rectal bleeding;	645 (2.2)	Primary care UK electronic records, f/u 2 yrs	yes	no	yes	yes
Robertson 2006 (34)	Prospective, 1996-1999, UK, primary care	604 with rectal bleeding	22 (3.6)	all FS, hospital records; f/u at least 4 yrs	no	no	yes	yes
Sanchez 2005 (85)	Prospective over three mths, Spain, primary care	126 with rectal bleeding with 63 over 50 yrs old	6 (4.8)	all colonoscopy	yes	no	yes	yes
Shapley 2010 (54)	Meta-analysis, UK, primary care	25 studies, 12 studies included in meta-analysis	various	various	various	various	various	various
Steine 1994 (92)	Prospective during 9-month period, Norway, Primary care	1852	55 (3.0)	all barium enema	yes	yes	yes	yes
Stellon 1997 (86)	Prospective over five-yr period, UK, primary care	26 over 50 yrs with iron deficiency anemia	2 (7.7)	26 had FS and 22 had DCBE	yes	no	yes	yes
Wauters 2000 (89)	Prospective, 1993-1994, Belgium, Primary care	386 with rectal bleeding	27 (7.0)	endoscopy in some cases, others not reported; CRC histologically confirmed; f/u 18-30 mths	yes	unclear	yes	unclear
Yates 2004 (41)	Retrospective from June 1997 to May 2001, UK	431 with IDA; excluded history of anemia within	37 (8.6)	various, f/u at least 12 mths	yes	no	yes	yes

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
		previous 12 mths or known hematologic abnormalities						

Abbreviations: Avg = average; CRC = colorectal cancer; CT = computed tomography; f/u = follow-up; FS = flexible sigmoidoscopy; Hb = hemoglobin; IBD = irritable bowel disease; IDA = iron-deficiency anemia; mths = months; No. = number; NR = not reported; 2WW = two-week wait; UK = United Kingdom; yr = year.

Table 5. Calculated median PPVs for signs or symptoms.

Study (sample size)	RB	RB first episode	RB & male	RB & female	RB ≥50 yrs or RB ≥55 yrs	RB ≥60 yrs or RB ≥65 yrs	RB ≥70 yrs or RB ≥75 yrs	RB dark	RB mixed with stool	RB & no perianal symptoms	RB & ABD pain	RB & WT loss	CBH or diarrhea	RB & CBH	RB & diarrhea	IDA	Wt loss	ABD pain
Parker 2007 (83) (n=29,007)	2.2	2.2			4.0	4.6	4.9											
Jones 2007 (76) (n=15,289)	2.2	2.2	2.4	2.0														
Hamilton 2005 (72) (n=2093)	2.4										3.1	4.7	0.94		3.4		1.2	1.1
Steine 2004 (92) (n=1852)	5.9												3.0				4.8	2.1
Flashman 2004 (71) (n=695)										10.6					13.9	10.9		
Robertson 2006 (34) (n=604)	3.6		4.8	2.7	5.7		7.5	7.4	5.4		1.7	4.8			4.8			
Muris 1993 (79) (n=578)																		0.5
Chohan 2005 (67) (n=462)										18			14		19	34		
Yates 2004 (41) (n=431)																8.6		
Heintze 2005 (21) (n=422)	4.0	4.0			5.6													
Norrelund 1996 (80) (n=417)	14	14	17	13			31				23	23		27				
Wauters 2000 (89) (n=386)	7.0				11	13	15					16						
Ellis 2005 (17) (n=319)	3.4	4.7				5.2		9.7	3.0	11				9.2	12			
Panzuto 2003 (82) (n=280)	16												12			41	36	13
Fitjen 1995 (70) (n=269)	3.3	5.2	5.9	1		20			14		2.2	9.5			9.0			

Study (sample size)	RB	RB first episode	RB & male	RB & female	RB ≥50 yrs or RB ≥55 yrs	RB ≥60 yrs or RB ≥65 yrs	RB ≥70 yrs or RB ≥75 yrs	RB dark	RB mixed with stool	RB & no perianal symptoms	RB & ABD pain	RB & WT loss	CBH or diarrhea	RB & CBH	RB & diarrhea	IDA	Wt loss	ABD pain
du Toit 2006 (69) (n=265)	5.7	5.7			6.1	8.6	7.9											
Helfand 1997 (73) (n=201)	6.5																	
Mant 1989 (77) (n=145)	10		9.1	13				17	21		9.3	14		11				
Barwick 2004 (13) (n=144)			16	5						6.9						11	5	7
Sanchez 2005 (n=126) (85)	4.8				9.5													
Metcalf 1996 (90) (n=99)	8.1	8.1						9.7	11		7.1	13		10	7.4			
Stellon 1997 (86) (n=26)																7.7		
Median across studies	**5.3**	**5.0**	**7.5**	**3.9**	**5.9**	**8.6**	**7.9**	**9.7**	**11**	**10.8**	**5.1**	**13**	**7.5**	**10.5**	**9**	**11**	**4.9**	**2.1**

Abbreviations: ABD = abdominal; CBH = change in bowel habits; IDA = iron-deficiency anemia; RB = rectal bleeding; Wt = weight; yrs = years.

Rectal Bleeding

Twenty-one studies provided PPVs on rectal bleeding as a single presenting symptom (13,17,21,24,34,65,67,69-73,76,77,80,82,83,85,89,90,92). Rectal bleeding as a broad classification had PPVs ranging from 2.2% to 16% in 16 studies, with a median value of 5.3% (Table 5) (17,21,34,69,70,72,73,76,77,80,82,83,85,89,90,92). Half of those studies had PPVs greater than or equal to 5% (69,73,77,80,82,85,89,90,92). Similarly, three meta-analyses calculated pooled PPVs for rectal bleeding between 5% and 8% (44,47,54).

The PPVs of rectal bleeding characterized as new was reported in eight studies and had a median of 4.95% (17,21,69,70,76,80,83,90). Ellis et al (2005) and Fitjen et al (1995) found that patients with a previous history of rectal bleeding had lower PPVs (3.8% and 0%, respectively) compared to rectal bleeding presented as a first episode (4.7% and 5.2%, respectively)(Appendix 4)(17,70).

Five of six studies found higher PPVs for males than for females, collapsed across all ages (13,34,70,76,77,80). The median PPV for males with rectal bleeding was 7.5%, ranging from 2.4% to 17%, whereas for females, the median PPV was calculated to be 3.9%, ranging from 1% to 13% (Table 5). In addition, PPVs for rectal bleeding tended to increase with age. Patients in their fifties or older with rectal bleeding had a median PPV of 5.9%, whereas patients in their sixties or older had a median PPV of 8.6% (Table 5)(17,21,34,69,70,83,85,89). Patients in their seventies or older with rectal bleeding had a median PPV of 7.9% for CRC (34,69,80,83,89). These findings likely reflect higher incidence rates of CRC from ages 60 to 79 (95). Both Lawrenson et al (2005) and Jones et al (2007) also observed increasing CRC with the increasing age of both males and females presenting with rectal bleeding; however, males had higher PPVs within each age group compared to females in the same age group (Appendix 4) (24,76). In addition, using multivariate analysis with a large sample of 29,007 patients with rectal bleeding, Parker et al (2007) found that the risk of CRC was strongly associated with age and was higher in males than in females (Appendix 14) (83).

Four studies examined rectal bleeding without anal symptoms such as hemorroids and found PPVs ranging from 6.9% to 18% with a median of 10.8% (Table 5) (13,17,67,71). Ellis et al found that bleeding and no perianal symptoms had a PPV of 11%, whereas bleeding with perianal symptoms had a PPV of only 2.0% (17).

The PPVs of rectal bleeding also varied depending on the colour or shade of blood and the location of blood in relation to stool. Four studies investigating dark rectal bleeding found PPVs from 7.4% to 17%, with a median PPV of 9.7% (Table 5) (17,34,77,90). The PPV of bright red blood in three of these studies ranged from 4.0% to 9.9% (17,77,90). Five studies with PPVs for rectal bleeding mixed with stool had a median of 11%, ranging from 3% to 21% (Table 5)(17,34,70,77,90). Robertson et al (2006) found higher PPV values when rectal blood was mixed with stool (5.4%) or was dark (7.4%) or was both mixed with stool and dark (10%), compared to when it was neither dark nor mixed with stool (1.9%) (34). Mant et al (1989) also found higher PPV values when rectal bleeding was dark (17%) or mixed with stool (21%), compared to when rectal bleeding was bright (9.9%) or separate from stool (6.6%) (77). Similarly, Metcalf et al (1996) found dark rectal bleeding had a higher PPV (9.7%) than bright rectal bleeding (8.6%), and Fijten et al (1995) found rectal bleeding mixed with stool had a higher PPV (14%) than did rectal bleeding seen on or mixed with stool (7%) (70,90). Furthermore, Ellis et al (2005) found dark rectal bleeding had a PPV of 9.7% compared to 4.0% for bright blood, although rectal blood mixed with stool had a PPV of 3% compared to 4.3% for rectal bleeding not mixed with stool (17).

In regression analysis, rectal bleeding (72,92), including blood mixed with stool (34,70), was a significant predictor of CRC in four studies. Three meta-analyses found higher specificity but lower sensitivity for dark rectal bleeding (minimum-maximum=sensitivity 15%-35%, specificity 84%-96%) (18,47,50). The high level of pooled specificity led Ford et al (2008) to

conclude that dark rectal bleeding would be useful in prioritizing patients for referral in primary care (18). Likewise, Jellema et al, using bivariate analysis, found that patients with dark rectal bleeding had a significantly higher risk of CRC than did those without dark rectal bleeding (47). They calculated a pooled PPV, from primary and secondary care studies, of 7% for rectal bleeding, 14% for dark rectal bleeding, and 6% for blood mixed with stool.

Olde Bekkink et al and Jellema et al found modest diagnostic performance for blood mixed with stool with higher specificity but lower sensitivity for CRC (sensitivity 40% and 51%, specificity 81% and 71%, respectively) (47,50). However, Olde Bekkink et al suggested this symptom should lead to referral for further investigation, because it nearly doubled the post-test probability of CRC (pooled likelihood ratio=1.91; 95% confidence interval [CI], 0.75 to 5.51) (50).

Change in Bowel Habits

Six studies provided information regarding change in bowel habits as predictors of CRC (24,67,71,72,82,92). Two studies investigated undefined or undifferentiated change in bowel habits (82,92), three studies investigated diarrhea (67,72,82), and two studies examined constipation (72,82). The PPV for change in bowel habits or diarrhea ranged from 0.94% to 14%, with a median of 7.5% (Table 5) (67,72,82,92). If PPVs were reported for change in bowel habits as well as diarrhea in any given study, the lesser PPV was included in the calculation. Based on Lawrenson et al (2005), the PPVs of change in bowel habit appear to increase with age and differ between men and women (24). The PPV for men at ten-year age bins was greater than 5% beginning at 60 years, whereas for women the PPV never exceeded 4.09% even in the oldest age group.

In regression analysis, change in bowel habits including constipation or diarrhea was found to be a significant predictor of CRC in three studies (70,72,80). One study examining the association between the characteristics of changes in bowel habit and risk of CRC found that loose stools significantly increased the risk of CRC compared to soft stools after adjusting for age, sex, and lifestyle variables (30). Frequency of bowel movement, stool quantity, feelings of discomfort, and laxative use were not significantly associated with risk of CRC.

All three meta-analyses found that change in bowel habits showed poor diagnostic performance (minimum–maximum=sensitivity 41%-62%, specificity 61%-69%) (18,47,50). Diarrhea or constipation as single symptoms showed poor diagnostic performance with slightly higher specificity ranging from 72% to 80% but a low sensitivity of 13% to 20% (18,47). Jellema et al calculated a pooled PPV of 9% for change in bowel habits and pooled PPVs of 6% for diarrhea or constipation (47). However, studies included from primary care selected for patients with rectal bleeding; therefore, the PPVs were for patients with rectal bleeding and change in bowel habits.

Anemia or Iron-Deficiency Anemia (IDA)

Nine studies provided PPVs for anemia or IDA as predictors of CRC (13,20,24,41,67,71,72,82,86). Hamilton et al (2005) and Hamilton et al (2008) provided PPVs for anemia for both men and women combined at two hemoglobin levels (100-130 g/L: PPV, 0.97%; <100 g/L: PPV, 2.3%; 100-129 g/L: PPV, 0.3%; <99 g/L: PPV=2.0%, respectively) (20,72). Two studies by Hamilton et al (2008) and Lawrenson et al (2005) had PPVs for anemia for men or women at different age groups (20,24). In both studies, PPVs generally increased with age and were higher in males than in females. The highest PPVs in the Lawrenson et al study were found among males with anemia aged 70-79 with a PPV of 3.38% and among women with anemia aged 80-89 with a PPV of 2.01% (24). In the Hamilton et al (2008) study, PPVs were higher than 5% in males or females greater than 60 years old, divided into ten-year age bins, and with hemoglobin levels less than 90 g/L (20). Males aged 60-69 or greater than 79 years and with

hemoglobin levels of 90-99 g/L also had PPVs greater than 5%. In most cases, these PPVs increased to greater than 10% if the patients had IDA as well. Four of six primary care studies that examined IDA in both males and females also found PPVs higher than 10% and ranged from 7.7% to 41%, with a median of 11% (Table 5)(13,41,67,71,82,86).

In regression analyses, three studies included anemia or IDA and associated features of iron deficiency in their regression models (20,72,82). Both Hamilton et al (2005, 2008) case-control studies found lower hemoglobin categories were significantly associated with increased CRC risk (20,72). Furthermore, microcytosis (mean cell or corpuscular volume [MCV] <80.0 fL) and low ferritin (<20 ng/mL) were both strongly associated with CRC (20). Panzuto et al (2003) also found IDA (Hb <140 g/L for males and <120 g/L for females, with ferritin <30 µg/L and MCV of <80 fL) to be a significant predictor of CRC (82).

All three meta-analyses found higher specificity for anemia and/or IDA but poorer sensitivity for either test (minimum-maximum=sensitivity 13%-23%, specificity 87%-95%) (18,47,50). Olde Bekkink et al found that IDA had the highest pooled likelihood ratio of 3.67 (95% CI, 1.30 to 10.35) of all signs or symptoms reported (50). They suggested that IDA was predictive of CRC and required further diagnostic testing.

Rectal or Abdominal Mass

Three studies provided PPVs for rectal or abdominal masses as predictors of CRC (13,67,71) and were all conducted in the UK in two-week referral clinics. Chohan et al (2005) and Flashman et al (2004) found PPVs greater than 10% for rectal or abdominal masses (67,71). Barwick et al (2004) found a PPV for CRC of 17% when patients had either an abdominal or rectal mass (13). A meta-analysis by Ford et al (2008) found that finding an abdominal mass had a high level of a pooled specificity of 96%, and they suggested that this alarm feature would be helpful in prioritizing patients for referral to a specialist (18).

Weight Loss

Four studies had PPVs for weight loss as a predictor of CRC (Table 5) (13,72,82,92). The PPVs ranged from 1.2% to 36% and had a median of 4.9%. In regression analysis, loss of weight was found to be a significant predictor in two studies (72,92). All three meta-analyses found high specificity (minimum-maximum=89%-91%) but low sensitivity for weight loss (minimum-maximum=17%-22%) (18,47,50). Jellema et al suggested that only weight loss had some diagnostic value because of its high specificity (47). They calculated a pooled PPV of 9%, but all studies from primary care selected for patients with rectal bleeding. Olde Bekkink et al proposed that weight loss should lead to referral for further investigation, because it almost doubled the post-test probability of CRC (pooled likelihood ratio, 1.89; 95% CI, 1.03 to 3.07) (50).

Abdominal Pain

Five studies had PPVs for abdominal pain or bloating as a predictor of CRC (13,72,79,82,92). For abdominal pain, PPVs ranged from 0.5% to 13%, with a median of 2.1% (Table 5). Astin et al 2011 calculated a pooled PPV with three studies of 3.29% (44). In regression analysis, abdominal pain and abdominal tenderness were each reported as significant predictors in Hamilton et al (2005) (72). Jellema et al found poor diagnostic performance and heterogeneity in sensitivity and specificity (pooled: sensitivity 35%, specificity 59%) across studies investigating abdominal pain (47). They calculated a pooled PPV of 5% from primary and secondary care studies. Olde Bekkink et al found poor diagnostic performance (pooled: sensitivity 25%, specificity 73%) and a lower positive-likelihood ratio for abdominal pain (0.94, 0.19-1.59) than for other symptoms (50).

Symptom Combinations

Ten studies provided PPVs for symptoms combinations (17,34,67,70-72,77,80,89,90). The Hamilton et al (2005) case-control study included a figure with PPVs for various symptom combinations (72) and found that all PPVs were higher when there was a combination of symptoms compared to the PPVs of single symptoms. The only exception was rectal bleeding and constipation, where the PPV remained unchanged compared to rectal bleeding as a single symptom (PPV=2.4%). PPVs for symptom combinations with a least three studies available are described below.

Rectal Bleeding and Change in Bowel Habit

Nine studies provided PPVs for rectal bleeding and change in bowel habits including diarrhea as presenting symptoms (Table 5)(17,34,67,70-72,77,80,90). Six of these studies selected for patients with rectal bleeding (17,34,70,77,80,90). Four studies included PPVs for rectal bleeding and change in bowel habits undefined (17,77,80,90). In all of these studies, PPVs were higher with the combination of rectal bleeding and change in bowel habits compared to rectal bleeding alone. The PPVs ranged from 9.2% to 27% and had a median of 10.5%. Similarly, Astin et al reported a pooled PPV of 11.8% (44). Seven studies reported PPVs for patients with rectal bleeding and diarrhea (17,34,67,70-72,90). The median PPV was 9% and ranged from 3.4% to 19%. Three studies found higher PPVs for the combination of rectal bleeding with diarrhea compared to rectal bleeding with constipation (17,72,90).

Rectal Bleeding and Weight Loss

Seven studies had PPVs for rectal bleeding and weight loss as a combination of symptoms (34,70,72,77,80,89,90). Six of these studies selected patients with rectal bleeding (34,70,77,80,89,90). In all of these studies, PPVs were higher with the combination of rectal bleeding and weight loss compared to rectal bleeding alone. The PPVs ranged from 4.7% to 23% and had a median of 13%. Astin et al 2011 also found a pooled PPV of 13.4% for this combination of symptoms (44).

Rectal Bleeding and Abdominal Pain

Six studies included PPVs for rectal bleeding and abdominal pain as presenting symptoms (34,70,72,77,80,90). Five of these studies selected for patients with rectal bleeding (34,70,77,80,90). For only two of the six studies, the combination of rectal bleeding and abdominal pain had a higher PPV compared to rectal bleeding alone. The PPVs ranged from 1.7% to 23%, with a median of 5.1%. Astin et al 2011 found a pooled PPV of 7.58% for rectal bleeding and abdominal pain (44).

Rectal Bleeding and Hemorrhoids

The PPVs for rectal bleeding with hemorrhoids were reported in three studies (34,70,77). All of these studies selected for patients with rectal bleeding. The PPVs were from 3.1% to 10%.

Summary/Interpretation

In summary, based on the a priori criteria of a PPV of 10%, FPs and other PCPs should make referrals for the following signs and symptoms considered predictive of CRC: dark rectal bleeding, rectal bleeding mixed with stool, rectal bleeding in the absence of perianal symptoms, rectal bleeding combined with change in bowel habits, rectal bleeding combined with weight loss, and IDA. The evidence also suggests that the PPVs of combinations of symptoms are higher than PPVs of single symptoms.

2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of CRC?

The study characteristics are listed in Table 6. The studies were from the updated literature search (done since the NZGG and NICE searches), the reference lists, and the NICE and NZGG reports (3,4). Since we did not specifically focus on PPVs for the diagnostic accuracy of tests, studies from secondary care were included. In addition, NICE and NZGG organized the data within the context of each study rather than each test; therefore, the data in this review are not easily compared to the data in those reviews (3,4). Colonoscopy is considered the gold standard for working up symptomatic patients with signs or symptoms suspicious of CRC. The following tests are compared to colonoscopy where possible to provide FPs and other PCPs with some perspective of test utility where colonoscopy is delayed or not possible. The outcomes from the studies can be found in Appendix 16.

Table 6. Study characteristics for clinical question about diagnostic tests for colorectal cancer.

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index/ standard	Missing/ uninterpre-table data explained	Withdrawals explained
Andersen 1991 (63)	Retrospective over 3-yr period, NZ, Secondary care	89 with CRC	89	SCBE or DCBE vs. colonoscopy	yes	no/no	yes	yes
Anderson 2011 (43)	Retrospective over 3-yr period, UK, primary and secondary care	978, excluded patients with cancers other than CRC	78 (8.0)	Pathology records 3 yrs following 2WW referral	yes	no/no	yes	Yes
Bjerregaard 2009 (45)	Prospective, Denmark, primary/secondary care	256 without CRC risk factors, aged 40 years or older presenting without visible rectal bleeding, referred by GP	8 (3.1)	Hemoccult Sensa® FOBT; either colonoscopy or FS, one patient had FS and DBCE/virtual colonoscopy; mean f/u 18.1 mths	no	no/yes	yes	yes
Brewster 1994 (66)	Retrospective over 3-yr period, UK, Primary & Secondary care	462	21 (4.5)	Barium enema and/or FS vs. colonoscopy	unclear	no/yes	yes	unclear
Chen 2006 (14)	Prospective from Jan 2001 to July 2004, Taiwan, Tertiary care	511 with abdominal distension	97 (19)	Ultrasonography vs. colonoscopy (for positive f/u); CT scan (for negative f/u); histologically confirmed	yes	yes/yes	yes	yes
Church 1991 (68)	Prospective, USA, Secondary care	269 with rectal bleeding	34 (13)	Barium enema (n=78) vs. colonoscopy	unclear	unclear/ no	no	yes
Duff 2006 (16)	Prospective, UK, Secondary care	112 symptomatic patients who could not undergo colonoscopy/ barium enema	8 (7.1)	CT colonography vs. 1-yr f/u (for negatives); endoscopic f/u (for positives)	yes	unclear/ yes	yes	yes
Fijten 1995 (70)	Prospective from Sept 1988 to Apr 1990, Netherlands, Primary care	269 with rectal bleeding	9 (3)	Endoscopy, radiography, sigmoidoscopy, proctoscopy, sonography; f/u at least 1 yr	yes	yes/ unclear	unclear	yes
Hamilton 2005 (72)	Case control, UK, Primary care records	349 cases, 1744 controls	349	Cancer registry	no	yes to case / control status	yes	yes

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index/ standard	Missing/ uninterpre-table data explained	Withdrawals explained
Helfand 1997 (73)	Prospective, USA, Primary care	201 with rectal bleeding (red blood in stool/on toilet paper during last 3 mths)	13 (6.5)	All sigmoidoscopy and barium enema, f/u 6-12 mths	no	no/yes	yes	yes
Irvine 1988 (74)	Prospective between Aug 1985 and Dec 1986, Canada, unclear	71 with rectal bleeding	5 (7.0)	FS or DCBE or colonoscopy vs. results on FS and DCBE and colonoscopy or histology	no	yes/yes	yes	yes
Jensen 1993 (75)	Prospective, Sweden, secondary care	149	5 (3.4)	Rectosigmoidoscopy and DCBE vs. surgical removal; 3-5 yr f/u	yes	No/yes	yes	Unclear
Koo 2006 (22)	Meta-analysis, UK, NR	6 studies, 1508 patients (frail and elderly)	various	Minimal preparation computed tomography vs. various reference standards; systematic review was not performed	various	various	various	various
Mant 1989 (77)	Prospective over 11-mth period, Australia, Primary care	145 age >40 yr with rectal bleeding; excluded IBD, CRC, polyposis coli, coagulation defect, hematologic disorder, melena	16 (11)	Mainly colonoscopy, some FS and air contrast barium enema; histopathology	yes	no/yes	yes	yes
Martinez-Ares 2005 (27)	Prospective from Sept to Dec 2003 and Jul to Oct 2004, Spain, Secondary care	145	43 (30)	Abdominal ultrasound vs. endoscopy, performed on same day or same hospital stay	yes	yes/yes	yes	yes
Martinez-Ares 2009 (49)	Prospective from Aug 2004 to Dec 2005, Spain, Secondary care	153 suspicious of CRC	70 (46)	Abdominal ultrasound vs. endoscopy, performed on same day or same hospital stay	no	yes/yes	yes	yes
McSherry 1969 (78)	Retrospective over 30-yr period, USA, Secondary care	1625 with CRC	1625	Hospital records, histologically confirmed	no	no/ unclear	no	yes
Oono 2010 (51)	Retrospective from June 2007 to June 2008, Japan, secondary care	1073	91 (8.5)	Immunochemical FOBT; colonoscopy	no	Unclear/yes	no	no
Ott 1989 (81)	Retrospective over 4-yr period, USA, unclear	128	12 (9.4)	Single or double barium enema vs. colonoscopy	yes	no/no	yes	yes
Rex 1990 (91)	RCT from Mar 1985 to Nov 1987, USA, Secondary and tertiary care	380 recruited with rectal bleeding, 168 completed FS + ACBE, 164 completed colonoscopy	22 (6.6)	Air contrast barium enema and FS vs. colonoscopy	no	no/no	yes	yes
Roberts-Thomson 2008 (35)	Prospective, Australia, Secondary care	202	9 (4.5)	CT colonography vs. colonoscopy, performed on same day	unclear	yes/yes	yes	yes
Robinson 2011 (52)	Retrospective, UK, Japan, China, secondary care	137 with CRC	137	CT colonography vs. histology on colonoscopic biopsy or surgically resected	yes	unclear/ no	unclear	unclear

Author	Study, country, setting	No. of patients	No. of patients with CRC (%)	Investigation used	Consecutive patients	Blinded to index/ standard	Missing/ uninterpre-table data explained	Withdrawals explained
				tumour or post-mortem examination				
Shaw 2009 (36)	Retrospective over 2-yr period, UK, Primary care 2WW	2159	unknown	Hemoccult® FOBT vs. cancer status from hospital database	yes	no/yes	unclear	unclear
Sofic 2010 (58)	Prospective, Bosnia and Hercegovina, secondary care	227 with history of blood in stool, anemia, constipation, changes in the stool or positive FOBT	56 (25)	All had CT colonography, barium enema and colonoscopy vs. histology	unclear	unclear	yes	Yes
Tate 1988 (87)	Prospective, UK, Primary or Secondary care	130 open-access colonoscopy; 100 hospital- referred colonoscopy; 100 GP- referred DCBE	14 (10.8); 7 (7); 3 (3)	DCBE vs. colonoscopy; histology performed	yes for hospital & GP referrals	no/yes	yes	yes
Taylor 2003 (88)	Prospective over 13-mth period, UK, Primary care	49	6 (12)	CT colonography vs. colonoscopy, performed on same day	yes	yes/yes	yes	yes
Thompson 2008 (37)	Prospective, UK, Secondary care	16,433 referrals in 15,363 patients over age 16 yrs	946 (6.2)	Mostly FS with barium enema/colonoscopy/ CT colonography/ ultrasonography vs. 3-yr f/u	yes	unclear/ yes	yes	yes
Tolan 2007 (38)	Retrospective over 14-mth period, UK, Secondary care	400 >70 yrs of age	30 (7.5)	CT colonography vs. radiology and laboratory reports after 12.5 mths	yes	unclear/ unclear	yes	yes
Viiala 2007 (39)	Retrospective over 2-yr period, Australia, Tertiary hospital	1632	65 (4)	FOBT; colonoscopy	no	unclear/ unclear	no	no
Wauters 2000 (89)	Prospective, Belgium, Primary care	386 with rectal bleeding	27 (7.0)	Endoscopy in some cases, other investigations NR; CRC histologically confirmed; f/u 18-30 mths	yes	unclear/ yes	yes	unclear
White 2009 (61)	Prospective between Jul 2002 and Apr 2004, USA, 2WW	150	18 (12)	CT colonography vs. colonoscopy (performed on same day) and operative/ pathological findings	no	yes/yes	yes	yes

Abbreviations: ACBE, = air contrast barium enema; CRC = colorectal cancer; CT = computed tomography; DCBE = double-contrast barium enema; FOBT fecal occult blood test; f/u = follow-up; FS = flexible sigmoidoscopy; GP = general practitioner; IBD - irritable bowel disease; mth = month; No. = number; NR = not reported; NZ = New Zealand; SCBE = single-contrast barium enema; 2WW = two- week wait; UK = United Kingdom; USA = United States of America; vs. = versus; yr = year.

Fecal Occult Blood Test (FOBT)

The Jellema et al meta-analysis investigated the diagnostic performance of FOBTs in patients symptomatic for CRC (47). Most of the studies were conducted in secondary care, and most of the studies did not specify the patients' symptoms. Although there was heterogeneity across the studies, the authors found good diagnostic performance with both guaiac-based tests (pooled sensitivity=75%, specificity=86%, PPV=28%, NPV=99%) and immunochemical-based tests (pooled sensitivity=95%, specificity=84%, PPV=21%, NPV=100%) in comparison to other indicators for CRC. Only one study, investigating guaiac-based tests, was conducted in the primary care setting. In subgroup analysis, immunochemical-based tests showed higher sensitivity than did

guaiac-based tests in detecting CRC. These results are in contrast to the NICE guidelines that recommend against the use of FOBTs in symptomatic patients because of poor diagnostic performance (3).

Five other studies found in the literature search were not included in Jellema et al (36,39,45,51,78). In a two-week-wait clinic, Shaw et al (2008) found a PPV of 7.7% for Hemoccult® FOBT, and in a tertiary care setting, Viiala et al (2007) found a PPV of 14.3% and an OR of 5.9 for FOBT (36,39). McSherry et al (1969) performed in a secondary care setting found a sensitivity of 73.3% for a guaiac-based FOBT (78). Using the Hemoccult Sensa® FOBT in primary or secondary care settings, Bjerregaard et al 2009 found a PPV of 10.5%, a NPV of 99.0%, a sensitivity of 75.0% and a specificity of 79.4% for the detection of CRC (45). Oono et al 2010 used an immunochemical FOBT in a secondary care setting and found for CRC a PPV of 33.7%, a NPV of 97.4%, a sensitivity of 74.7%, a specificity of 86.4%, a positive-likelihood ratio of 5.48, a negative-likelihood ratio of 0.29 and an odds ratio of 18.7 (51).

Digital Rectal Examination (DRE)

A case-control study by Hamilton et al (2005) found a PPV of 1.5% for an abnormal rectal examination for CRC (72). However, when an abnormal rectal examination was combined in turn with one of six symptoms, four of those symptoms, including rectal bleeding, diarrhea, loss of weight and abdominal tenderness, in combination with the abnormal rectal examination resulted in PPVs greater than 5%. A prospective study of patients with rectal bleeding by Fijten et al found that the PPVs for CRC increased when a rectal palpation found a hemorrhoid (n=2/20, PPV=10%) versus DRE found an abnormal prostate (n=1/2, PPV=50%) versus DRE found a palpable tumour (n=1/1, PPV=100%), although these PPVs were based on small numbers (70). As well, in patients selected for rectal bleeding, a palpable tumour had a PPV of 32% for CRC (89).

Proctoscopy and Blood Work

Fijten et al found that an abnormal proctoscopy had a sensitivity of 0%, a specificity of 30%, a PPV of 0%, and an NPV of 87% for the detection of CRC (70). However, proctoscopy was performed by FPs in only 17% (n=45) of the patients, and only two had CRC. They also found that the hemoglobin, ESR, and white blood cell count had low sensitivity in detecting CRC (cited in NICE and NZGG) for the 225 patients with laboratory test results (3,4,70). However, the PPV for low hemoglobin was 14%; for low ESR, 9%; for high ESR, 17%; and for high white blood cell count, 12%.

Ultrasound

Martinez-Ares et al (2005) compared abdominal ultrasound with colonoscopy in 145 consecutive symptomatic patients and found a sensitivity of 79% and a specificity of 92% (27). Multivariate analysis including age, sex, hemoglobin, hematocrit, and MCV counts, clinical presence of low digestive hemorrhage, constitutional syndrome, altered bowel habit, and results of the sonography in the model found only positive ultrasonography (OR, 9.26; 95% CI, 4.8 to 17.5) and the presence of microcytosis in blood tests (OR, 2.16; 95% CI, 1.34 to 3.46) were independent factors predicting CRC. Similar results were obtained in a subsequent study by Martinez-Ares et al (2009) (49). The accuracy of ultrasonography for diagnosing CRC among patients suspected of having CRC was 83%, the sensitivity 83.3%, specificity 82.7%, PPV 78.5% and NPV 86.7%.

Chen et al (2006) investigated 511 consecutive patients with abdominal distension and compared ultrasonography to colonoscopy or CT scans (14). They found a sensitivity of 93%, a specificity of 99%, a PPV of 95%, and an NPV of 98%.

Computed Tomography (CT) Colonography

Seven studies investigated the diagnostic accuracy of CT colonography for CRC among symptomatic patients (16,35,38,52,58,61,88). One study was performed in a primary care setting in the UK using the two-week-wait rules (88), and another study had referrals mainly from the two-week-wait clinics (61). The five other studies were performed in secondary care settings, and it was unclear whether the symptomatic patients were referred from primary care (16,35,38,52,58). As well, three studies had less than 10 patients diagnosed with CRC (16,35,88), one had 18 patients (61), one retrospective study had 30 patients (38), one prospective had 56 patients (58), and one reviewed 137 patients with CRC (52). Taylor et al (2003) found that CT colonography detected five of six cancers (83%) compared to colonoscopy (88). Roberts-Thomson et al (2008) found that five of nine (56%) cancers confirmed histologically were considered probable cancers with CT colonography, and three of 193 (NPV=98%) lesions were false positives for CRC (35). In Sofic et al 2010, all 56 cases of CRC were found using CT colonography that had a sensitivity, specificity and PPV of 100% (58). Duff et al (2006) investigated 112 symptomatic patients who could not undergo colonoscopy or barium enema (16). Patients were followed for 12 months. They found a sensitivity of 87.5% and a specificity of 97.1% for the detection of CRC. The White et al (2009) prospective study found a sensitivity of 100% and specificity of 99.2% for virtual colonoscopy compared to colonoscopy (61). Tolan et al (2007) retrospectively reviewed 400 consecutive symptomatic patients older than 70 years and undergoing CT colonography over a 14-month period (38). The sensitivity of CT colonography for the detection of CRC was 93%. Using computer-aided detection for CT colonography, Robinson et al 2011 also found a sensitivity of 93.6% for CRC among symptomatic patients (52).

Minimal-Preparation Computed Tomography (CT)

One meta-analysis that did not systematically review the literature found a pooled sensitivity of 83% and a pooled specificity of 90% from six studies with symptomatic patients for the detection of CRC using minimal-preparation CT (22).

Barium Enema and/or Sigmoidoscopy

There were twelve studies that examined the diagnostic validity of barium enema or sigmoidoscopy (37,43,58,63,66,68,73-75,81,87,91). One study included patients referred from primary care (68), five from secondary care (37,58,63,73,75), three from both primary and secondary care (43,66,87), one from secondary and tertiary care (91), and two undetermined (74,81). Tate (1988) found that the diagnostic yield from GP-referred open-access barium enemas (3%) was lower than the diagnostic yield in hospital-referred colonoscopy patients (7%) or open-access colonoscopy patients (11%) (87). Anderson et al 2011 found the diagnostic accuracy of surgical assessment for CRC was significantly better than general practitioners' assessment due to the surgeons' use of rigid sigmoidoscopy (43). Among patients referred for rectal bleeding, air-contrast barium enema had a sensitivity of 75%, a specificity of 43%, a PPV of 71%, and an NPV of 47% for the detection of CRC compared to colonoscopy (68). Ott et al (1989) found that barium enema correctly diagnosed 12 (100%) carcinomas identified with colonoscopy, and Anderson et al (1991) found a sensitivity of 71% for single-contrast barium enema or DCBE compared with colonoscopy (63,81). Sofic et al 2010 found a sensitivity of 94.6% and a specificity and PPV of 100% for barium enema compared to colonoscopy (58). As well, for patients referred for colonoscopy from primary care due to rectal bleeding, the sensitivity was higher for DCBE (92%) than for rigid sigmoidoscopy (77%), performed by the investigators, and highest when both tests were used (100%) (73). Also, Jensen et al 1993 found a higher sensitivity for DCBE than for rigid sigmoidoscopy (75). Rex et al (1990) found no difference in the proportion of patients diagnosed with colon cancer when patients, referred for lower

gastrointestinal bleeding, were randomized to air-contrast barium enema and FS versus colonoscopy (91). Similarly, for patients referred for rectal bleeding, DCBE (83%) and a combination of DCBE and FS (83%) had higher sensitivity than did FS alone (67%) (74). Brewster et al (1994) also found that DCBE (100%) had higher sensitivity than did FS, performed by specialists, when compared against colonoscopy (52%) (66). However, for patients followed for three years, Thompson et al (2008) found that FS (99%), carried out by colorectal surgeons or general practice specialists, had a higher sensitivity than did DCBE (86%) (37).

Carcinoembryonic Antigen (CEA)

A European guideline on the diagnostic use of tumour markers for CRC, cited by NICE and NZGG, included sensitivity and specificity for CEA but only in healthy subjects (3,4,96). No additional primary studies were found that included the diagnostic parameters of CEA among symptomatic patients.

Summary/Interpretation

In summary, based on the review of the evidence of the diagnostic accuracy of investigations for CRC, the Working Group has identified the following tests as having a place in the investigative workup for CRC by FPs and other PCPs: FOBTs, CT colonography, barium enema, and sigmoidoscopy.

3. What major, known risk factors increase the likelihood of CRC in patients presenting with signs and/or symptoms of CRC?

The evidence table for this question can be found in Appendices 14 and 17. The NICE systematic review suggested that ulcerative colitis is a risk factor for CRC, but this was not specific to symptomatic patients (3). In addition, evidence was lacking that a family history of hereditary nonpolyposis colon cancer was a risk factor in symptomatic patients (3). Although the NZGG review listed several risk factors for CRC, the supporting evidence was from screening studies or studies conducted in the general population and not among symptomatic patients (4). Therefore, it cannot be concluded from the NICE or NZGG reports that any of the risk factors should raise the suspicion of CRC in symptomatic patients.

The meta-analysis by Olde Bekkink et al found a pooled positive-likelihood ratio of 1.05, a pooled sensitivity of 15% and a pooled specificity of 85% for patients with a family history of CRC (50). These were based on three studies that selected patients with rectal bleeding (21,70,77). Likewise, Jellema et al included two studies from primary care and four from secondary care and found consistently high specificity (pooled specificity=91%) but variable sensitivity (pooled sensitivity=16%) for a family history of cancer among symptomatic patients (47,77,90). They also reported a pooled PPV of 6% and a pooled NPV of 96%.

One study by Steine et al (1994), which was not found in NICE (2), NZGG (3) or the meta-analyses, examined the risk of a personal or family history of CRC and/or polyps among referred patients (92). Those authors found a low PPV for patients with a first-degree relative with CRC or polyps (1.3%) and a higher PPV with patients with a personal history of CRC or polyps (5.7%) (92).

There were four studies that included risk factors in multiple-regression analysis (34,70,83,92). In the regression models of Fijten et al and Steine et al (1994), a family history of cancer or abdominal disease was not a significant predictor of CRC (70,92). As well, a patient's report of irritable bowel syndrome was not found to be a predictive factor for CRC in the Robertson et al (2006) regression analysis (34). The Parker et al (2007) multivariate analysis by a Cox proportional hazards model found that smoking and coronary heart disease lowered the rate of CRC among patients with rectal bleeding followed for two years (83). However, it is unclear whether patient CRC status was verified at the end of the two-year period.

Summary/Interpretation

Based on the PPVs from the evidence, it seems that a family history of cancer does not increase the risk of CRC among symptomatic patients. However, because there were few studies conducted in primary care among an unselected patient population, and the degree of relatedness of the family history was not always well defined across studies, strong conclusions could not be derived.

4. Which factors are associated with delayed referral? Which factors influence delay by patient and which, delay by physician? Does a delay in the time to consultation affect patient outcome?

The NICE guidelines included a systematic review for delay that included one other systematic review and 18 primary observational studies (3). The main findings indicate that patient-related delay in diagnosis is mostly associated with patients' beliefs about their symptoms, including patients not knowing the importance of bowel symptoms or thinking that bleeding is not serious or is caused by hemorrhoids. The second most common reason for patient delay is the fear that the resultant tests may be unpleasant or embarrassing. Delay was decreased if patients experienced symptoms that produced considerable initial discomfort and embarrassment, or had abdominal pain, nausea, or vomiting. For FP-related delay, not recognizing symptoms suggestive of colon carcinoma and failure to investigate IDA or to perform a rectal examination at the first consultation have been associated with increased delay. In addition, initial referral to a specialist without a gastrointestinal interest increased delay. No relationship was found between socio-economic status (SES), gender, or ethnicity and diagnostic delay.

The NZGG guideline includes a systematic review for delay for all suspected cancers (4). The articles that were specific to CRC supported the NICE evidence-based conclusions.

A systematic review by Mitchell et al (2008) included 169 articles from primary or secondary care settings and also supported many of the conclusions derived in the NICE guideline (28). In addition, this systematic review found other factors that influenced delay. For patient-related delay, those with co-morbidity tended to delay less, and those with rectal cancer delayed more than did those with colon cancer. Although SES was not found to influence delay, social support was found to decrease delay, and rural residence or lower levels of education were found to increase delay. For practitioner-related delay, receiving inaccurate or inadequate tests resulted in increased delay. Patients who visited their FP more frequently after an inconclusive initial visit experienced an increase in delay. Older patients or patients with rectal cancer were generally referred more quickly.

A prospective Danish observational study (n=459, colon cancer; n=289, rectal cancer) found that female colon cancer patients had a longer patient delay than did male cases, but the reverse was seen for rectal cancer patients (23). Secondary analysis of the UK National Survey of NHS Cancer Patients, using general linear modelling, found that single and separated/divorced people had longer pre-hospital delays than did married people (29). For referral delay, females had longer delays than did males, younger people had longer delays than did older people, and Black and South Asian people had longer delays than did Caucasians (29).

A prospective study of 280 consecutive Italian patients from primary care found no significant difference in patient- or physician-related delay between patients with or without CRC (82). Likewise, a prospective Norwegian study of 1852 consecutive patients from primary care found no difference between patient delay and the detection of cancer, but physician delay in patients with CRC was significantly shorter than was delay in patients without CRC (92).

Shabbir et al (2009) conducted a retrospective review of patients under the age of 50 years presenting with CRC (53). They found that only 24% were referred through the two-week-wait clinics, which had the shortest median time from referral to initial consultation. Seventy-five percent of the patients would have been eligible for the two-week-wait clinics if age were not a deciding factor in the NICE recommendations. They suggested removing age as a one of the criterion for referral.

Similar to the NICE conclusions, Damery et al 2011 found that the median time to CRC diagnosis for patients with IDA was shorter if they were referred to relevant surgical and gastroenterological specialists (including colorectal and general surgery) compared to other medical specialties (46).

A retrospective study in the USA of 289 symptomatic and asymptomatic patients with CRC found that abnormal symptoms, laboratory tests or imaging results were associated with shorter delays between referral and diagnosis, and the presence of family history (without symptoms or abnormal screening) had longer delays between referral and diagnosis (40).

Singh et al (2009) retrospectively reviewed records of patients diagnosed with CRC whose primary care physicians were within a tertiary care facility (55). They evaluated missed opportunities to initiate endoscopic evaluation based on a set of predefined clinical signs, symptoms, and diagnostic tests. They found a mean of 4.2 missed opportunities and 5.3 clues per patient for the 161 patients with missed opportunities. Suspected or confirmed IDA was the most common clue associated with missed opportunities. Also, African-Americans or patients with congestive heart failure or coronary artery disease were more likely to experience missed opportunities. In logistic regression analysis, patients greater than 75 years of age or patients with anemia were more likely to experience missed opportunities, and patients with abnormal FS or CT scans were less likely to have missed opportunities.

For missed opportunities related mostly to the primary care physician, Singh et al confirmed the results of the NICE report and the Mitchell et al systematic reviews (3,28,55). Additional factors observed included when diagnostic tests were ordered but not performed and when diagnostic or laboratory tests were inadequately followed up, especially with positive FOBTs or complete blood counts (55).

Another study by Singh et al (2011) reviewed patients with CRC at a tertiary care setting over a six-year period (57). They found shorter wait times from referral to colonoscopy for patients with three diagnostic signs or symptoms compared to one sign or symptom. Referrals marked as urgent or next available had shorter wait times than did those marked as routine. As well, documented verbal discussion between the referring physician and the consultant resulted in shorter wait times. Signs and symptoms associated with wait times greater than 60 days included IDA, abnormal CT scan or barium enema, suspected mass on physical examination, abdominal pain, and obstruction. A positive FOBT, hematochezia, and history of polyps were associated with wait times of less than 60 days.

Five articles were found that discussed wait times in Canada (19,25,31,56,64). Armstrong et al (2008) conducted a week-long audit across Canada of consecutive patients seen for consultation or a procedure by a specialist physician (64). In Ontario, the median wait time to consultation for 2480 audits was 72 days. The median wait time from referral to completion of procedures or tests with a digestive health provider for 774 audits was 110 days. For patients with alarming features (n=316), the median wait time from the patient's first referral until completion of the procedures or tests was 62 days compared to 153 days for patients without alarming features (n=372). A retrospective study conducted in Manitoba found the median diagnostic delay from the last visit with the referring physician to a diagnosis of CRC increased from 44 to 64 days over a five-year period (2001-2005) (56). Also, the median delay from contact with the referring physician to the first colonoscopy increased from 37 to 54 days over the same time period (56). A retrospective observational study of 350 patients conducted in The Ottawa

Hospital found that the median time from referral for symptoms suggestive of CRC to a confirmed diagnosis was 66 days. In addition, patients with CRC had significantly shorter delays between referral and the time when patients were informed of their diagnosis than did patients without CRC (19). No associations were found between age, sex, comorbidity, or referring physician and the interval from referral to patient being informed of their diagnosis.

Consensus recommendations for wait times in Canada were developed by the Canadian Association of Gastroenterology using a modified Delphi approach (31). They recommended that patients with acute gastrointestinal bleeding should be seen by a specialist, and if indicated, endoscoped within 24 hours; patients with a high likelihood of cancer based on imaging or physical examination should be seen by a specialist, and if indicated, endoscoped within two weeks; and patients with bright red rectal bleeding or documented IDA or one or more positive FOBTs or chronic constipation or chronic diarrhea or a new-onset change in bowel habit or chronic unexplained abdominal pain should be seen by a specialist, and if indicated, endoscoped within two months.

A week-long audit of specialists across Canada compared the wait times from the patient's first referral until the completion of procedures or tests to the target wait times recommended by the Canadian Association of Gastroenterology (25). In Ontario, the median wait time for patients with a high likelihood of cancer based on imaging or physical examination was 28 days; for patients with documented IDA, 56 days; for patients with one or more positive FOBTs, 83 days; and for patients with unexplained diarrhea or chronic constipation, 139 days. Fifteen to 52% of people were seen within the target wait time in Ontario.

Two meta-analyses by Ramos et al (2007, 2008) suggest there is no association between diagnostic delay and survival in patients with CRC (n=8 studies, 3680 patients) or disease stage at the time that the diagnosis is made (n=17 studies, 2509 patients) (32,33). However, when colon and rectal cancer are analyzed separately (n=4 studies, 1001 patients with colon cancer, 799 with rectal cancer), a shorter delay is associated with more advanced disease for patients with colon cancer, but the opposite was seen for patients with rectal cancer (32,33).

This is supported by Wattercheril et al (2008), who found no association between the delay between referral and CRC diagnosis and mortality when the reason for the referral, the stage of CRC at diagnosis, or the type of CRC treatment were included in the model (40). Similarly, no relationship was found between diagnostic delay and early stage CRC but for late stage CRC, specifically Dukes D tumours, a shorter delay was associated with shorter survival (59). As well, Rupassara et al (2006) found patients who waited 50 days or more between referral and diagnosis had better cancer-specific five-year survival (p=0.007) than did patients waiting less than 50 days during that interval (84). A retrospective observational study by Comber (2005) found survival was better for patients with longer wait times than for those waiting less than a month (15). Torring et al 2011 also found mortality decreased with increasing diagnostic intervals but only until approximately five weeks, after which time mortality increased (60).

Summary/Interpretation

Patient-related factors that were found to have the most influence on delay were patients not recognizing the significance of their symptoms as suggestive of CRC or the fear of the possible tests or interventions that might occur. Patients with more severe symptoms or other co-morbidities were found to have a decrease in delay. As well, those patients with social support had shorter delays. FP-related factors included physicians not recognizing the symptoms of CRC in their patients or not investigating IDA or performing a rectal examination. In addition, referral to a specialist without a gastrointestinal interest or receiving inadequate test results lead to a delay. Although SES overall appeared not to have a significant effect on

delay, several papers found that a lower level of education, living in a rural area, being single/divorced, female, Black or South Asian, or younger led to an increase in delay.

DISCUSSION

Signs and symptoms that may raise suspicions of CRC were evaluated and compared to the predictability of the FOBT used in the Ontario population-based CRC screening program, ColonCancerCheck (PPV=10.9%) (2). The following symptoms yielded median PPVs greater than 10% in primary care settings: dark rectal bleeding, rectal bleeding mixed with stool, rectal bleeding in the absence of perianal symptoms, rectal bleeding combined with change in bowel habits, rectal bleeding combined with weight loss, and IDA. All studies examining abdominal or rectal mass had PPVs greater than 10%. A combination of the symptoms or signs with other symptoms generally increased the PPVs. As well, increasing age elevated PPVs. Signs or symptoms also tended to have higher PPVs in males than in females.

For diagnostic tests for CRC, colonoscopy is considered the gold standard and would be performed by a specialist. However, if there is a delay to consultation with a specialist, there is some evidence to suggest that CT colonography, barium enema, or sigmoidoscopy may be good alternative techniques in the interim. The sensitivities and/or specificities were over 83% when CT colonography or barium enema were compared to colonoscopy (16,35,37,38,52,58,61,63,66,73,74,81,88). FS also showed good sensitivity for detecting CRC, especially when combined with DCBE (37,66,74,91). There were few studies examining the diagnostic accuracy of abdominal CT, abdominal or pelvic ultrasound, DRE, proctoscopy, a CBC, or CEA among symptomatic patients. Also, the potential risks of these alternative techniques were not considered in this review.

The evidence also suggests that the FOBT is a good predictor of CRC based on the studies conducted mainly in secondary care settings with symptomatic patients. In patients presenting with suspicious signs or symptoms of CRC, a meta-analysis showed good diagnostic performance for both immunochemical and guaiac-based FOBTs (47). For those patients that have symptoms of CRC leading to referral, a FOBT may not be useful if it does not influence the specialist's urgency for consultation with the patient. However, in patients presenting with signs or symptoms that are recommended as not requiring urgent or semi-urgent referral, FOBTs may be useful in helping to determine if the patient has occult bleeding in addition to other signs or symptoms that could lead to a referral.

Two meta-analyses found high specificity but low sensitivity for CRC for symptomatic patients with a family history of cancer (47,50). Jellema et al reported a pooled PPV of 6% for patients with a family history of cancer, and Steine et al found a PPV of 5.7% for patients with a personal history of CRC or polyps (47,92). It appears that the PPV for patients with a family history of cancer may not be substantially higher than with other signs or symptoms. However, these patients would normally participate in a CRC surveillance program, which includes regular colonoscopies.

In addition to factors associated with delay reported in NICE or NZGG, this review also found that patients with social support had shorter delays, and physicians receiving inadequate or inaccurate results led to a delay (3,4,28). Furthermore, although NICE reported that there was no relationship found between SES, gender, or ethnicity and diagnostic delay, this review found evidence that a lower level of education, living in a rural area, being single/divorced, female, Black or South Asian, or younger led to an increase in delay (3,23,28,29,55).

Three papers report that the wait times in Ontario for patients with symptoms or signs of CRC are longer than the proposed wait times suggested by the Canadian Association of Gastroenterology (19,25,31,64). Leddin et al (2008) found only 15% to 52% of symptomatic patients in Ontario were seen within the target wait times (25). Although the evidence suggests

that delay in referral does not have an impact on patient survival, the psychological morbidity on patients and their families should be considered.

CONCLUSIONS

Using a PPV of 10% as a threshold, patients with an abdominal or rectal mass should be referred urgently, and dark rectal bleeding, rectal bleeding mixed with stool, rectal bleeding in the absence of perianal symptoms, rectal bleeding combined with change in bowel habits, rectal bleeding combined with weight loss, or IDA should be referred to a specialist competent in endoscopy semi-urgently (2). The target wait times for endoscopy set by the Canadian Association of Gastroenterology can be used as a guide for referral (31).

FOBTs showed good diagnostic performance for CRC among symptomatic patients and may be ordered in cases where symptoms do not lead to urgent or semi-urgent referral and there is a low suspicion of CRC (47). For symptomatic patients who are waiting a substantial amount of time for a consultation with a specialist, CT colonography, barium enema, or sigmoidoscopy may be alternative investigative measures to consider. The results of any interim tests should be made available to the specialists to help them prioritize patients.

To reduce the delay in referral, there should be appropriate education of patients and FPs and PCPs in the signs and symptoms of CRC. FPs and PCPs should assess patients for signs and symptoms of CRC at periodic health examinations and should counsel patients to address common fears and concerns. Special efforts should be made to address challenges in groups with known delays in CRC diagnosis.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Colorectal Cancer Referral Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Suzie Joanisse received a grant from CCO to develop a program to increase breast, colorectal, and cervical screening in Aboriginal communities. Sara Kaune provides guidance to FPs and other PCPs in the referral of patients for colonoscopy and has received funding from CCO for the start-up and operation of a gastrointestinal diagnostic assessment program. All other authors declared no conflicts of interest.

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A complete list of the members of the Working Group, with their affiliations and conflict of interest information, is provided in Section 2. Appendix 1.

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Appendix 1. Members of the Colorectal Cancer Referral Working Group, Expert Panel, and Targeted Peer Reviewers.

Colorectal Cancer Referral Working Group	
Chair: Lisa Del Giudice MD CCFP FCFP Primary Care Practitioner Sunnybrook Family Practice Unit, Toronto, ON	Cheryl Levitt MBBCh CCFP FCFP Provincial Primary Care Lead Cancer Care Ontario, Toronto, ON
Amanda Hey MD CCFP FCFP Regional Primary Care Lead Hôpital régional de Sudbury Regional Hospital - Regional Cancer Program, Sudbury, ON	William Harris MD FRCSC Surgeon Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON
Marko Simunovic MD Surgical Oncologist Juravinski Cancer Centre, Hamilton, ON	Emily Vella PhD Research Coordinator Program in Evidence-based Care, Cancer Care Ontario, Hamilton, ON
Colorectal Cancer Referral Expert Panel	
Rob Annis Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Sara Kaune Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Marla Ash Regional Primary Care Lead, Cancer Care Ontario, Central, ON	Gregory Knight Gastrointestinal Disease Site Group, CCO Grand River Regional Cancer Centre, Kitchener, ON
Praveen Bansal Regional Primary Care Lead, Cancer Care Ontario, Central West and Mississauga Halton, ON	Hugh Langley Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Carole Beals Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Doina Lupea Program Manager Primary Care Cancer Care Ontario
Christine Brezden-Masley Gastrointestinal Disease Site Group, CCO St. Michael's Hospital, ON	Heather McLean Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Sandy Buchman Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Alison McMullen Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Lynn Chappell Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Michael Mills Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Charles Cho Gastrointestinal Disease Site Group, CCO Southlake Regional Health Centre, ON	Julia Niblett Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
John Day Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Jason Pantarotto Gastrointestinal Disease Site Group, CCO The Ottawa Hospital Regional Cancer Centre, ON
Lee Donohue Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Raimond Wong Associate Professor, McMaster University Department of Oncology - Division of Radiation Oncology
Danusia Gzik Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Sophie Wilson Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Suzie Joanisse Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Sheila-Mae Young Regional Primary Care Lead, Cancer Care Ontario, Central East, ON

Sindu Kanjeekal Gastrointestinal Disease Site Group, CCO Windsor Regional Hospital, ON	
Colorectal Cancer Referral Targeted Peer Reviewers	
Anna Kobylecky General Surgeon St. Catharines, ON	Bob Bluman Clinical Professor, Department of Family Medicine University of British Columbia

Appendix 2. List of sites searched for the environmental scan.

CMA Infobase
The Physicians Query Database (National Cancer Institute)
National Guideline Clearing House
NICE (UK) – NICE Guidance
SIGN (UK) – SIGN Guidelines
ASCO (US) – ASCO Guidelines
NCCN (US) – NCCN home (consensus-based)
National Health and Medical Research Council (Aus) – Cancer Guidelines
New Zealand Guidelines Group - Guidelines

Appendix 3. Literature search strategies.

Signs MEDLINE

(2004-2007 using NICE terms)

Database: Ovid MEDLINE(R) <1996 to June Week 2 2009> Search Strategy:

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1 exp "sensitivity and specificity"/ (239327)
2 false negative reactions/ or false positive reactions/ (12654)
3 (sensitivity or specificity or accura$).ab,ti. (441413)
4 diagnos$.ab,ti. (629674)
5 predictive value$.ab,ti. (31069)
6 reference value$.ab,ti. (4999)
7 ROC.ab,ti. (8755)
8 (likelihood adj ratio$1).ab,ti. (4069)
9 monitoring.tw. (125815)
10 (false adj (negative$1 or positive$1)).ab,ti. (22852)
11 double-blind method/ or single-blind method/ (65827)
12 (randomized controlled trial or controlled clinical trial).pt. (205799)
13 consensus development conference$.pt. (4866)
14 practice guideline.pt. (10940)
15 review.pt. (914918)
16 review.ab. (312258)
17 (meta-analysis or metaanalysis).ab. (14991)
18 meta-analysis.pt. (18597)
19 meta-analysis.ti. (9102)
20 (cohort adj stud$).ab,ti. (35083)
21 exp cohort studies/ (449951)
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (51879)
23 or/1-22 (2463187)
24 letter.pt. (344350)
25 editorial.pt. (157352)
26 comment.pt. (290185)
27 or/24-26 (554903)
28 23 not 27 (2398165)
29 (loss adj2 appetite).tw. (1161)
30 Anorexia/ (1903)
31 "nausea and vomiting"/ or nausea/ or vomiting/ (9965)
32 gastrointestinal hemorrhage/ or melena/ (9795)
33 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw. (35)
34 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw. (2538)
35 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw. (8023)
36 ((mucus or pass$ mucus) adj stool$).tw. (5)
37 stips$.tw. (6)
38 exp Diarrhea/ (13033)
39 frequency of defecation.tw. (86)
40 ((foecal or fecal) and incontinen$).tw. (1700)
41 continen$.tw. (11740)
42 constipat$.tw. (6619)
43 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw. (44616)
44 sign$.tw. (1991139)
45 symptom$.tw. (314869)
46 or/29-45 (2236624)

47 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or exp liver neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/ (120262)
48 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (74388)
49 or/47-48 (137774)
50 (200406: or 200407: or 200408: or 200409: or 20041: or 2005: or 2006: or 200701: or 200702: or 200703: or 200704: or 200705: or 200706: or 200707:).ed. (1964383)
51 50 and 28 and 49 and 46 (7279)
52 limit 51 to (english language and humans) (6264)

(2007-2009 including NICE and NZ terms)
Database: Ovid MEDLINE(R) <1996 to June Week 1 2009> Search Strategy:
---
1 exp "sensitivity and specificity"/ (238835)
2 false negative reactions/ or false positive reactions/ (12638)
3 (sensitivity or specificity or accura$).ab,ti. (440620)
4 diagnos$.ab,ti. (628511)
5 predictive value$.ab,ti. (31012)
6 reference value$.ab,ti. (4992)
7 ROC.ab,ti. (8735)
8 (likelihood adj ratio$1).ab,ti. (4062)
9 monitoring.tw. (125521)
10 (false adj (negative$1 or positive$1)).ab,ti. (22820)
11 double-blind method/ or single-blind method/ (65711)
12 (randomized controlled trial or controlled clinical trial).pt. (205454)
13 consensus development conference$.pt. (4846)
14 practice guideline.pt. (10918)
15 review.pt. (913358)
16 review.ab. (311457)
17 (meta-analysis or metaanalysis).ab. (14956)
18 meta-analysis.pt. (18546)
19 meta-analysis.ti. (9069)
20 (cohort adj stud$).ab,ti. (34992)
21 exp cohort studies/ (449028)
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (51792)
23 or/1-22 (2458631)
24 letter.pt. (343817)
25 editorial.pt. (156938)
26 comment.pt. (289558)
27 or/24-26 (553839)
28 23 not 27 (2393743)
29 exp body weight changes/ (24344)
30 (weight adj1 loss$).tw. (22311)
31 exp "signs and symptoms, digestive"/ (45562)
32 cachexia.tw. (2258)
33 (loss adj2 appetite).tw. (1160)
34 early satiety.tw. (346)
35 Anorexia/ (1903)
36 anorexia.tw. (8602)
37 "nausea and vomiting"/ or nausea/ or vomiting/ (9941)
38 nausea.tw. (18123)
39 vomiting.tw. (19020)
40 gastrointestinal hemorrhage/ or melena/ (9783)

41 ((abdom$ or stomach or back or flank) adj3 pain).tw. (30542)
42 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw. (35)
43 ((abdom$ or stomach or rect$ or colorectal or renal or intestin$ or gastrointestin$) adj3 mass$).tw. (6304)
44 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw. (2534)
45 obstruction$.tw. (40441)
46 ((gastrointestina$ or intestin$) adj (bleed$ or hemorrhag$ or haemorrhag$)).tw. (6160)
47 gastrointestinal hemorrhage/ or melena/ (9783)
48 ((rect$ or colorect$) adj3 (bleed$ or hemorrhag$ or haemorrhag$)).tw. (1475)
49 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw. (8012)
50 ((mucus or pass$ mucus) adj stool$).tw. (5)
51 stips$.tw. (6)
52 (melena or maelena).tw. (587)
53 Hematuria/ (2822)
54 (hematuria or haematuria).tw. (5863)
55 (hematochezia or haematochezia).tw. (472)
56 exp anemia/ (36706)
57 (anemia or anaemia).tw. (35322)
58 (iron adj deficiency adj (anemia or anaemia)).tw. (2519)
59 exp Jaundice/ (1908)
60 jaundice.tw. (7205)
61 exp Diarrhea/ (13014)
62 (diarrhea or diarrhoea).tw. (26781)
63 change$ in bowel habit$.tw. (137)
64 bowel habit change$.tw. (11)
65 frequency of defecation.tw. (86)
66 ((foecal or fecal) and incontinen$).tw. (1699)
67 continen$.tw. (11718)
68 constipat$.tw. (6606)
69 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw. (44538)
70 exp Cholecystitis/ (2615)
71 cholecystitis.tw. (3053)
72 Ascites/ (3480)
73 ascites.tw. (8958)
74 Hepatomegaly/ (1060)
75 (hepatomegaly or hepato megaly).tw. (2125)
76 (alarm adj1 (symptom$ or sign$)).tw. (382)
77 sign$.tw. (1987256)
78 symptom$.tw. (314320)
79 or/29-78 (2353258)
80 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or exp liver neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/ (120049)
81 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (74248)
82 or/80-81 (137527)
83 28 and 82 and 79 (27248)
84 limit 83 to (english language and humans) (22545)
85 (200708: or 200709: or 20071: or 2008: or 2009:).ed. (1266739)
86 84 and 85 (4692)

Signs EMBASE
(2004 – 2006 using NICE terms)
Database: EMBASE <1996 to 2009 Week 25>
Search Strategy:
---
1 "sensitivity and specificity"/ (52914)
2 false negative result/ or false positive result/ (4811)
3 (sensitivity or specificity or accura$).ab,ti. (413725)
4 diagnos$.ab,ti. (610737)
5 predictive value$.ab,ti. (30258)
6 reference value$.ab,ti. (4919)
7 ROC.ab,ti. (8247)
8 (likelihood adj ratio$1).ab,ti. (3807)
9 monitoring.tw. (122864)
10 (false adj (negative$1 or positive$1)).ab,ti. (21684)
11 double blind procedure/ or single blind procedure/ or triple blind procedure/ (60280)
12 exp controlled clinical trial/ (151465)
13 exp practice guideline/ (146078)
14 review.pt. (724011)
15 review.ab. (301585)
16 (meta-analysis or metaanalysis).ab. (14125)
17 Meta Analysis/ (31966)
18 meta-analysis.ti. (8926)
19 (cohort adj stud$).ab,ti. (33709)
20 cohort analysis/ (52287)
21 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (53250)
22 or/1-21 (1997077)
23 letter.pt. (307811)
24 editorial.pt. (182743)
25 or/23-24 (490554)
26 22 not 25 (1951870)
27 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw. (52)
28 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw. (2246)
29 ((gastrointestina$ or intestin$) adj (bleed$ or hemorrhag$ or haemorrhag$)).tw. (6129)
30 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw. (7834)
31 ((mucus or pass$ mucus) adj stool$).tw. (5)
32 stips$.tw. (9)
33 frequency of defecation.tw. (76)
34 ((foecal or fecal) and incontinen$).tw. (1673)
35 continen$.tw. (10491)
36 constipat$.tw. (7090)
37 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw. (43746)
38 sign$.tw. (1869627)
39 symptom$.tw. (320359)
40 or/27-39 (2103782)
41 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp liver cancer/ or exp intestine cancer/ or exp liver tumor/ or exp intestine tumor/ (134075)
42 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (72376)
43 or/41-42 (145005)

44 (2004: or 2005: or 2006: or 200701: or 200702: or 200703: or 200704: or 200705: or 200706: or 200707:).ew. (1756601)
45 40 and 43 and 26 and 44 (6919)
46 limit 45 to (human and english language) (5872)

(2007-2009 including NICE and NZ terms)
Database: EMBASE <1996 to 2009 Week 23>
Search Strategy:
---
1 "sensitivity and specificity"/ (52544)
2 false negative result/ or false positive result/ (4754)
3 (sensitivity or specificity or accura$).ab,ti. (411971)
4 diagnos$.ab,ti. (608490)
5 predictive value$.ab,ti. (30140)
6 reference value$.ab,ti. (4900)
7 ROC.ab,ti. (8205)
8 (likelihood adj ratio$1).ab,ti. (3777)
9 monitoring.tw. (122377)
10 (false adj (negative$1 or positive$1)).ab,ti. (21610)
11 double blind procedure/ or single blind procedure/ or triple blind procedure/ (60063)
12 exp controlled clinical trial/ (150877)
13 exp practice guideline/ (145627)
14 review.pt. (722049)
15 review.ab. (300216)
16 (meta-analysis or metaanalysis).ab. (14046)
17 Meta Analysis/ (31900)
18 meta-analysis.ti. (8854)
19 (cohort adj stud$).ab,ti. (33473)
20 cohort analysis/ (52003)
21 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (53059)
22 or/1-21 (1989882)
23 letter.pt. (306429)
24 editorial.pt. (182039)
25 or/23-24 (488468)
26 22 not 25 (1944903)
27 weight reduction/ (34934)
28 (weight adj1 loss$).tw. (21269)
29 Cachexia/ (3115)
30 cachexia.tw. (2199)
31 (loss adj2 appetite).tw. (1092)
32 early satiety.tw. (361)
33 Anorexia/ (18392)
34 anorexia.tw. (8440)
35 "nausea and vomiting"/ or nausea/ or vomiting/ (89020)
36 nausea.tw. (18994)
37 vomiting.tw. (19441)
38 abdominal pain/ or lower abdominal pain/ (36335)
39 digestive system hemorrhage/ or exp gastrointestinal hemorrhage/ or exp duodenum bleeding/ (22783)
40 ((abdom$ or stomach or back or flank) adj3 pain).tw. (31655)
41 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw. (52)
42 ((abdom$ or stomach or rect$ or colorectal or renal or intestin$ or gastrointestin$) adj3 mass$).tw. (5938)
43 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw. (2241)

44 obstruction$.tw. (39665)
45 ((gastrointestina$ or intestin$) adj (bleed$ or hemorrhag$ or haemorrhag$)).tw. (6114)
46 ((rect$ or colorect$) adj3 (bleed$ or hemorrhag$ or haemorrhag$)).tw. (1478)
47 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw. (7792)
48 ((mucus or pass$ mucus) adj stool$).tw. (5)
49 stips$.tw. (9)
50 (melena or maelena).tw. (678)
51 Hematuria/ (9476)
52 (hematuria or haematuria).tw. (5393)
53 (hematochezia or haematochezia).tw. (453)
54 exp anemia/ (74850)
55 (anemia or anaemia).tw. (33350)
56 (iron adj deficiency adj (anemia or anaemia)).tw. (2314)
57 exp Jaundice/ (10589)
58 jaundice.tw. (6721)
59 exp Diarrhea/ (64037)
60 (diarrhea or diarrhoea).tw. (24888)
61 change$ in bowel habit$.tw. (129)
62 bowel habit change$.tw. (8)
63 frequency of defecation.tw. (76)
64 ((foecal or fecal) and incontinen$).tw. (1672)
65 continen$.tw. (10452)
66 constipat$.tw. (7072)
67 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw. (43580)
68 exp Cholecystitis/ (3891)
69 cholecystitis.tw. (2556)
70 exp Ascites/ (9664)
71 ascites.tw. (8490)
72 Hepatomegaly/ (4068)
73 (hepatomegaly or hepato megaly).tw. (1988)
74 (alarm adj1 (symptom$ or sign$)).tw. (398)
75 sign$.tw. (1861833)
76 symptom$.tw. (319234)
77 or/27-76 (2304715)
78 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp liver cancer/ or exp intestine cancer/ or exp liver tumor/ or exp intestine tumor/ (133493)
79 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (72080)
80 or/78-79 (144370)
81 (2007: or 2008: or 2009:).ew. (5941853)
82 77 and 80 and 26 (27787)
83 81 and 82 (8558)
84 limit 83 to (human and english language) (7568)

Test MEDLINE
(2004-2009)
Database: Ovid MEDLINE(R) <1996 to June Week 1 2009> Search Strategy:
---
1 Primary Health Care/ (24656)
2 Physicians, Family/ (7162)
3 ((family or general) adj practitioner$).mp. (16487)

4 gp.mp. (13693)
5 family physician$.mp. (4805)
6 family doctor$.mp. (1767)
7 Family Practice/ (27039)
8 ((family or general) adj practice$).mp. (34800)
9 primary care.mp. (33200)
10 primary health care.mp. (27461)
11 or/1-10 (92878)
12 meta-analysis/ (18546)
13 "review literature".mp. (2793)
14 meta-analy$.mp. (32391)
15 metaanal$.mp. (900)
16 (systematic$ adj (review$ or overview$)).mp. (17875)
17 meta-analysis.pt. (18546)
18 review.pt. (913358)
19 review.ti. (81648)
20 or/12-19 (954186)
21 Case Reports/ (598333)
22 letter.pt. (343817)
23 historical article.pt. (87049)
24 comment.pt. (289558)
25 editorial.pt. (156938)
26 or/21-25 (1155958)
27 20 not 26 (868875)
28 exp "sensitivity and specificity"/ (238835)
29 (sensitivity or specificity).tw. (284728)
30 exp Diagnostic Errors/ (39443)
31 predictive value$.tw. (31012)
32 "Predictive value of tests"/ (73110)
33 ROC.tw. (8735)
34 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw. (7318)
35 (false adj (negative or positive)).tw. (19547)
36 accuracy.tw. (88282)
37 reference value$.tw. (4992)
38 likelihood ratio$.tw. (4074)
39 ((pre-test or pretest) adj probability).tw. (659)
40 post-test probability.tw. (180)
41 Diagnosis, differential/ (148016)
42 Diagnostic tests, routine/ (3202)
43 or/28-42 (683007)
44 exp Blood Cell Count/ (41124)
45 (CBC or FBC or full blood count).tw. (1336)
46 C-reactive protein/ (13872)
47 c-reactive protein$.mp. (20546)
48 Blood sedimentation/ (2072)
49 erythrocyte sedimentation rate.mp. (3612)
50 ferritin.mp. or Ferritins/ (8531)
51 serum iron.mp. (1443)
52 Occult blood/ (1659)
53 stool occult blood.mp. (28)
54 faecal occult blood.mp. (342)
55 (fob or fobt).mp. (746)
56 Carcinoembryonic Antigen/ (3968)
57 Carcinoembryonic Antigen.tw. (3911)
58 Carcinogenic embryonic Antigen.tw. (5)

59 cea.tw. (6331)
60 Colonography, computed tomographic/ (955)
61 (ct scan adj2 abdom$).tw. (775)
62 virtual colography.mp. (1)
63 virtual colonography.mp. (26)
64 virtual colonoscopy.mp. (392)
65 Proctoscopy/ or proctoscopy.mp. (579)
66 anoscopy.mp. (93)
67 Sigmoidoscopy/ or sigmoidoscopy.mp. (2147)
68 barium enema.mp. (1261)
69 ultrasound.mp. or Endosonography/ (68656)
70 Digital rectal examination/ (223)
71 ((per rect$ or pr) adj exam$).tw. (18)
72 or/44-71 (154952)
73 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/ (81670)
74 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (65061)
75 73 or 74 (97352)
76 27 or 43 (1475839)
77 75 and 72 and 76 (3716)
78 (200406: or 200407: or 200408: or 200409: or 20041: or 2005: or 2006: or 2007: or 2008: or 2009:).ed. (3231122)
79 77 and 78 (1732)

Test EMBASE
(2004-2009)
Database: EMBASE <1996 to 2009 Week 24>
Search Strategy:
---
1 exp Primary health care/ (38099)
2 general practitioner/ (25890)
3 ((family or general) adj practitioner$).mp. (31879)
4 gp.mp. (21848)
5 Family physician/ (25890)
6 family physician$.mp. (4813)
7 family doctor$.mp. (1342)
8 general practice/ (16883)
9 ((family or general) adj practice$).mp. (22558)
10 primary care.mp. (29683)
11 primary health care.mp. (10136)
12 or/1-11 (101139)
13 Meta Analysis/ (31927)
14 "systematic review"/ (26933)
15 (meta-analy$ or metaanaly$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (41444)
16 (systematic adj (review$ or overview$)).mp. (34716)
17 review.pt. (723099)
18 review.ti. (79028)
19 or/13-18 (786457)
20 letter.pt. (307009)
21 editorial.pt. (182377)
22 or/20-21 (489386)

23 19 not 22 (780355)
24 "sensitivity and specificity"/ (52736)
25 sensitivity.tw. (200481)
26 specificity.tw. (123738)
27 "prediction and forecasting"/ (1429)
28 predictive value$.tw. (30192)
29 predictive value$ of test$.tw. (26)
30 roc curve/ (2196)
31 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw. (6890)
32 exp diagnostic error/ (20894)
33 (false adj (positive or negative)).tw. (18639)
34 diagnostic accuracy/ (111198)
35 accuracy.tw. (82007)
36 reference value/ (10114)
37 reference value$.tw. (4908)
38 likelihood ratio$.tw. (3801)
39 ((pre-test or pretest) adj probability).tw. (652)
40 post-test probability.tw. (171)
41 differential diagnosis/ (82196)
42 or/24-41 (522010)
43 exp blood cell count/ (59069)
44 (CBC or FBC or full blood count).tw. (1234)
45 c-reactive protein.mp. or C Reactive Protein/ (29435)
46 erythrocyte sedimentation rate/ (8447)
47 erythrocyte sedimentation rate.mp. (9050)
48 ferritin.tw. or Ferritin blood level/ or Ferritin/ (9751)
49 serum iron.mp. or exp Iron Blood Level/ (3073)
50 occult blood/ (2008)
51 faecal occult blood.tw. (331)
52 (fob or fobt).tw. (748)
53 Carcinoembryonic Antigen.tw. (3767)
54 Carcinogenic embryonic Antigen.tw. (4)
55 Carcinoembryonic Antigen/ (7624)
56 CEA.tw. (6366)
57 virtual colography.tw. (1)
58 virtual colonography.mp. (24)
59 virtual colonoscopy.mp. (378)
60 computer assisted tomography/ (181559)
61 computed tomographic colonography/ (1344)
62 (ct scan adj2 abdom$).tw. (727)
63 barium enema.mp. or Barium Enema/ (3475)
64 Rectoscopy/ or proctoscopy.tw. (591)
65 anoscopy/ or anoscopy.mp. (99)
66 Ultrasound/ or ultrasound.mp. (89568)
67 Sigmoidoscopy/ or sigmoidoscopy.tw. (3412)
68 Digital rectal examination/ (1461)
69 pr exam$.tw. (2)
70 per rectum exam$.tw. (7)
71 or/43-70 (370153)
72 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp intestine cancer/ or exp intestine tumor/ (91716)
73 exp Abdominal Tumor/ (8492)
74 72 or 73 (98646)
75 42 or 23 (1236650)
76 74 and 75 and 71 (6240)

77 limit 76 to (human and english language) (5303)
78 (2004: or 2005: or 2006: or 2007: or 2008: or 2009:).ew. (3204715)
79 77 and 78 (3375)

Delay MEDLINE

Database: Ovid MEDLINE(R) <1996 to June Week 2 2009> Search Strategy:

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1 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/ (81821)
2 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (74388)
3 or/1-2 (106394)
4 (delay$ adj3 practitioner$).tw. (31)
5 (delay$ adj3 diagnos$).tw. (7049)
6 (delay$ adj3 patient$).tw. (5005)
7 (diagnos$ adj1 delay$).tw. (2670)
8 (diagnos$ adj earl$).tw. (1436)
9 early diagnosis/ (4663)
10 earl$ diagnosis.tw. (19673)
11 (earl$ adj detect$).tw. (16059)
12 (earl$ adj present$).tw. (487)
13 (earl$ adj symptom$).tw. (992)
14 exp health behavior/ (44373)
15 exp attitude to health/ (145652)
16 Physician-patient relations/ (24283)
17 or/4-16 (222597)
18 "referral and consultation"/ (21157)
19 referral$.tw. (30725)
20 (late$ adj refer$).tw. (338)
21 (earl$ adj refer$).tw. (732)
22 Disease progression/ (58293)
23 Time factors/ (353063)
24 Physician's practice patterns/ (23294)
25 or/18-24 (468457)
26 (200709: or 20071: or 2008: or 2009:).ed. (1221727)
27 3 and 17 and 25 and 26 (128)
28 limit 27 to (english language and humans) (118)

Delay EMBASE

Database: EMBASE <1996 to 2009 Week 25>
Search Strategy:

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1 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp intestine cancer/ or exp intestine tumor/ (91910)
2 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw. (72376)
3 or/1-2 (110569)
4 Cancer diagnosis/ (40282)
5 early diagnosis/ (32872)
6 (earl$ adj diagnos$).tw. (20455)
7 diagnos$ earl$.tw. (1443)

8 Delayed Diagnosis/ (1221)
9 (delay$ adj3 diagnos$).tw. (7080)
10 (diagnos$ adj1 delay$).tw. (2687)
11 (delay$ adj3 practitioner$).tw. (19)
12 Patient attitude/ (18992)
13 Attitude to health/ or Attitude to illness/ or Illness behavior/ (4525)
14 (delay$ adj3 patient$).tw. (4818)
15 earl$ detection.tw. (14904)
16 (detect$ adj earl$).tw. (2804)
17 (earl$ adj present).tw. (2)
18 (earl$ adj symptom$).tw. (976)
19 or/4-18 (123986)
20 patient referral/ (25096)
21 referral$.tw. (27880)
22 (earl$ adj refer$).tw. (686)
23 (late$ adj refer$).tw. (300)
24 Time factors/ (49865)
25 exp disease course/ (733980)
26 25 and (5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 22 or 23) (23076)
27 clinical practice/ (79089)
28 or/20-24,26-27 (189950)
29 3 and 19 and 28 (1782)
30 (2007: or 2008: or 2009:).ew. (1461499)
31 29 and 30 (521)
32 limit 31 to (human and english language) (444)

Risk Factors MEDLINE
Database: Ovid MEDLINE(R), EMBASE
Search Strategy:
---
1 exp colorectal neoplasms/ (62183)
2 exp large intestine tumor/ (77984)
3 ((proximal or ascending or descending or transverse) adj colon adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (942)
4 ((colon$ or colorect$ or bowel$ or large bowel$ or intestin$ or pelv$ or abdom$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (119155)
5 ((sigmoid$ or rectosigmoid$ or jejunum or ileum or ileal or cecum or cecal or ileocecal or ileocecal junction or ICJ or appendi$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (4076)
6 CRC.tw. (7894)
7 Burkitt$ lymph$.tw. (4684)
8 (hereditary nonpolyposis colon cancer or nonpolyposis colon cancer or HNPCC or Lynch$ syndrome).tw. (3617)
9 exp primary health care/ (74886)
10 (primary care or primary health care).tw. (70266)
11 Family Practice/ (43871)
12 Physicians, Family/ (33024)
13 (family practi$ or family doctor$ or family physician$ or gp$ or general practi$).tw. (154404)
14 (200406: or 200407: or 200408: or 200409: or 20041: or 2005: or 2006: or 2007: or 2008: or 2009:).ed. (3217656)
15 meta-analysis.pt,sh. (50415)
16 (meta-anal$ or metaanal$).tw. (43171)
17 (quantitativ$ review$ or quantitativ$ overview$).tw. (627)
18 (systematic$ review$ or systematic$ overview$).tw. (34780)

19 (methodologic$ review$ or methodologic$ overview$).tw. (242)
20 (integrative research review$ or research integration$).tw. (61)
21 quantitativ$ synthes$.tw. (259)
22 (medline or medlars).tw,sh. or embase.tw. (58281)
23 (scisearch or psychinfo or psycinfo).tw. (4367)
24 (psychlit or psyclit).tw. (1161)
25 (hand search$ or manual search$).tw. (5229)
26 (electronic database$ or bibliographic database$).tw. (6497)
27 (pooling or pooled analys$ or mantel haenszel).tw. (11497)
28 (peto or der simonian or dersimonian or fixed effect$).tw. (4881)
29 review.pt,sh. or review$.tw. or overview$.tw. (2103635)
30 or/9-13 (263513)
31 or/22-28 (77707)
32 or/15-21 (93632)
33 29 and 31 (55841)
34 32 or 33 (126070)
35 or/1-8 (178711)
36 35 and 34 (3057)
37 limit 36 to english language (2800)
38 limit 37 to humans (2759)
39 38 and 14 (658)
40 remove duplicates from 39 (652)

Risk Factors EMBASE

Database: EMBASE <1996 to 2009 Week 25>
Search Strategy:
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1 exp colorectal neoplasms/ (1808)
2 exp large intestine tumor/ (78329)
3 ((proximal or ascending or descending or transverse) adj colon adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (484)
4 ((colon$ or colorect$ or bowel$ or large bowel$ or intestin$ or pelv$ or abdom$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (58845)
5 ((sigmoid$ or rectosigmoid$ or jejunum or ileum or ileal or cecum or cecal or ileocecal or ileocecal junction or ICJ or appendi$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw. (2029)
6 CRC.tw. (3937)
7 Burkitt$ lymph$.tw. (2276)
8 (hereditary nonpolyposis colon cancer or nonpolyposis colon cancer or HNPCC or Lynch$ syndrome).tw. (1795)
9 exp primary health care/ (38190)
10 (primary care or primary health care).tw. (33042)
11 Family Practice/ (16893)
12 Physicians, Family/ (25929)
13 (family practi$ or family doctor$ or family physician$ or gp$ or general practi$).tw. (76192)
14 meta-analysis.pt,sh. (31966)
15 (meta-anal$ or metaanal$).tw. (21443)
16 (quantitativ$ review$ or quantitativ$ overview$).tw. (299)
17 (systematic$ review$ or systematic$ overview$).tw. (17079)
18 (methodologic$ review$ or methodologic$ overview$).tw. (113)
19 (integrative research review$ or research integration$).tw. (22)
20 quantitativ$ synthes$.tw. (123)
21 (medline or medlars).tw,sh. or embase.tw. (30387)
22 (scisearch or psychinfo or psycinfo).tw. (1709)
23 (psychlit or psyclit).tw. (430)

24 (hand search$ or manual search$).tw. (2233)
25 (electronic database$ or bibliographic database$).tw. (2890)
26 (pooling or pooled analys$ or mantel haenszel).tw. (5487)
27 (peto or der simonian or dersimonian or fixed effect$).tw. (1899)
28 review.pt,sh. or review$.tw. or overview$.tw. (975354)
29 or/9-13 (126226)
30 or/21-27 (38983)
31 or/14-20 (52986)
32 28 and 30 (27428)
33 31 or 32 (69330)
34 or/1-8 (94839)
35 34 and 33 (1956)
36 limit 35 to english language (1781)
37 limit 36 to humans (1752)
38 (2004: or 2005: or 2006: or 2007: or 2008: or 2009:).ew. (3218100)
39 38 and 37 (1236)

Appendix 4. Rectal bleeding (RB) as a single symptom.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Rectal bleeding	Ellis 2005	RB	3.4 (1.9-6.1)
	Fitjen 1995	RB: new or history of RB	3.3 (1.7-6.3)
	Hamilton 2005	RB	2.4 (1.9-3.2)
	Helfand 1997	RB: red blood in stool/on toilet paper past 3 mths	6.5 (3.8-11)
	Mant 1989	RB	10 (6.3-16)
	Panzuto 2003	RB	16 (10-24)
	Robertson 2006	RB	3.6 (2.4-5.5)
	Sanchez 2005	RB	4.8 (2.2-10.2)
	Steine 1994	RB	5.9 (3.7-9.3)
	Wauters 2000	RB: Rectal blood on stool, underwear, toilet paper, irrespective of duration	7.0 (4.6-10)
First episode	du Toit 2006	RB: New irrespective of diarrhea/duration/anal causes	5.7 (3.4-9.2)
	Ellis 2005	First time bleeding	4.7 (2.0-11)
	Fijten 1995	RB: first time	5.2 (2.7-9.7)
	Heintze 2005	RB: First sign of RB	4.0 (2.5-6.4)
	Jones 2007	RB in three years after first RB	2.2 (2.0-2.5)
	Metcalf 1996	RB: first presentation of less than 1 yr duration	8.1 (4.1-15)
	Norrelund 1996	RB: new	14 (11-19)
	Parker 2007	RB: first-ever consultation	2.2 (2.1-2.4)
With no perianal symptoms	Barwick 2004	RB and no anal symptoms >65 yrs; pts under 2WW referral	6.9
	Chohan 2005	RB and no anal symptoms >55 yrs, pts under 2WW referral	18 (14-24)
	Ellis 2005	RB & no perianal symptoms	11 (5.4-22)
	Flashman 2004	RB and no anal symptoms >60 yrs; pts under 2WW referral	10.6 (6.7-16)
Dark/fresh/bright	Ellis 2005	Dark blood	9.7 (3.2-26)
	Ellis 2005	Bright blood	4.0 (2.0-7.8)
	Mant 1989	Dark blood	17 (6.7-38)
	Mant 1989	Bright blood	9.9 (5.7-17)
	Metcalf 1996	Dark blood	9.7 (3.2-26)
	Metcalf 1996	Bright blood	8.6 (3.9-18)
	Robertson 2006	Dark blood	7.4 (3.9-14)
Mixed with stool	Ellis 2005	Blood mixed with stool	3.0 (0.4-19)
	Ellis 2005	Blood not mixed with stool	4.3 (2.3-7.8)
	Fijten 1995	Blood seen mixed with stool only	14 (3.6-43)
	Fijten 1995	Blood seen on stool or mixed with only	7.4 (2.8-18)
	Mant 1989	Blood seen mixed with feces	21 (11-36) $p<0.05$

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
	Mant 1989	Blood separate from feces	6.6 (2.8-15)
	Metcalf 1996	Blood mixed with stool	11 (4.6-24)
	Robertson 2006	Blood mixed with stool	5.4 (3.4-8.5)
	Robertson 2006	Blood both dark and mixed with stool	10 (5.4-19)
	Robertson 2006	Neither dark nor mixed with stool	1.9 (0.8-4.6)
Blood on paper	Ellis 2005	Blood on paper only	2.4 (0.6-9.2)
	Ellis 2005	Blood in pan and on paper	4.9 (2.6-9.1)
	Mant 1989	Blood on paper only	9.6 (4.1-21)
	Metcalf 1996	Blood on paper only	8.3 (2.1-28)
Other	Ellis 2005	RB & perianal symptoms	2.0 (0.7-5.1)
	Ellis 2005	Large volume of blood	1.3 (0.2-8.4)
	Ellis 2005	Small volume of blood	5.3 (2.9-9.7)
	Ellis 2005	Not first time bleeding	3.8 (1.7-8.1)
	Fijten 1995	Blood seen – others or combinations	0.8 (0.1-5.6)
	Fijten 1995	Blood seen – unknown	7.4 (2.8-18)
	Fijten 1995	Previous history of rectal bleeding	0
	Hamilton 2005	RB reported twice	6.8
By Age/Gender	Barwick 2004	RB & female	5 (2-12)
	Barwick 2004	RB & male	16 (9-28)
	Bat 1992	RB & ≥80 yrs	29
	du Toit 2006	RB & ≥55 yrs	6.1 (3.6-10)
	du Toit 2006	RB & ≥65 yrs	8.6 (5-15)
	du Toit 2006	RB & ≥75 yrs	7.9 (3.6-16)
	Ellis 2005	RB & ≥60 yrs	5.2 (2.6-10)
	Ellis 2005	RB & ≤59 yrs	1.8 (0.6-5.5)
	Fijten 1995	RB, ≥60 yrs	20 (10-35)
	Fijten 1995	RB, female	1 (0.3-5.1)
	Fijten 1995	RB, male	5.9 (2.9-12)
	Heintze 2005	RB, <50 yrs; First sign of RB	1.3 (0.3-5.1)
	Heintze 2005	RB, ≥50 yrs; First sign of RB	5.6 (3.4-9.1)
	Jones 2007	CRC in men in 3 yrs after first rectal bleeding	2.4 (2.1-2.8)
	Jones 2007	CRC in women in 3 yrs after first rectal bleeding	2.0 (1.7-2.3)
	Jones 2007	RB, women <45yr*	0.2 (0.1-0.5)
	Jones 2007	RB, women 45-54 yr*	0.6 (0.3-1.2)
	Jones 2007	RB, women 55-64 yr*	2.8 (1.9-3.8)
	Jones 2007	RB, women 65-74 yr*	2.4 (1.6-3.5)
	Jones 2007	RB, women 75-84 yr*	7.2 (5.6-9.1)

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
	Jones 2007	RB, women ≥85 yr*	2.8 (1.5-4.8)
	Jones 2007	RB, men <45yr*	0.1 (0.02-0.3)
	Jones 2007	RB, men 45-54 yr*	1.6 (1.00-2.3)
	Jones 2007	RB, men 55-64 yr*	3.4 (2.5-4.5)
	Jones 2007	RB, men 65-74 yr*	4.8 (3.7-6.2)
	Jones 2007	RB, men 75-84 yr*	7.7 (5.8-10)
	Jones 2007	RB, men ≥85 yr*	5.1 (2.6-9.8)
	Lawrenson 2005	RB men aged 40-49**	0.92
	Lawrenson 2005	RB men aged 50-59**	2.75
	Lawrenson 2005	RB men aged 60-69**	5.99
	Lawrenson 2005	RB men aged 70-79**	7.69
	Lawrenson 2005	RB men aged 80-89**	9.13
	Lawrenson 2005	RB women aged 40-49**	0.87
	Lawrenson 2005	RB women aged 50-59**	2.16
	Lawrenson 2005	RB women aged 60-69**	3.50
	Lawrenson 2005	RB women aged 70-79**	4.61
	Lawrenson 2005	RB women aged 80-89**	4.89
	Mant 1989	RB & male	9.1 (4.4-18)
	Mant 1989	RB & female	13 (7.0-24)
	Norrelund 1996	RB & >69	31 (22-40)
	Norrelund 1996	RB & female	13 (9-18)
	Norrelund 1996	RB & male	17 (12-24)
	Parker 2007	RB: first-ever consultation & ≥55 yrs	4.0 (3.7-4.3)
	Parker 2007	RB: first-ever consultation & ≥65 yrs	4.6 (4.2-5.1)
	Parker 2007	RB: first-ever consultation & ≥75 yrs	4.9 (4.3-5.6)
	Robertson 2006	RB & ≥50 yrs	5.7 (3.7-8.7)
	Robertson 2006	RB & ≥70 yrs	7.5 (3.8-14)
	Robertson 2006	RB & female	2.7 (1.4-5.1)
	Robertson 2006	RB & male	4.8 (2.8-8.0)
	Sanchez 2005	RB & >50 yrs	9.5 (4.3-19.6)
	Wauters 2000	RB & <50 yrs	0.7 (0.1-4.9)
	Wauters 2000	RB & ≥50 yrs	11 (7-15)
	Wauters 2000	RB & ≥60 yrs	13 (9-19)
	Wauters 2000	RB & ≥70 yrs	15 (9-22)

Abbreviations: CI = confidence intervals; CRC = colorectal cancer; mth(s) = month(s); pts = patients; PPV = positive-predictive value; 2WW = two-week wait; yr(s) = year(s).
* CRC diagnosed within 3 yrs after first rectal bleed.
**Diagnosed within 12 mths of initial bleeding per 100 pts presenting (men & women).

Appendix 5. Change in bowel habits (CBH) as a single symptom.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
CBH	Panzuto 2003	CBH: Diarrhea or constipation or altered stool in previous 3 mths	15 (7.2-26)
	Steine 1994	CBH	3.0 (2.1-4.5)
Diarrhea	Chohan 2005	CBH (looser and/or more frequent) > 6 wks, pts under 2WW referral	14 (9.5-19)
	Hamilton 2005	Diarrhea	0.94 (0.7-1.1)
	Panzuto 2003	Diarrhea	12 (6.4-21)
Constipation	Hamilton 2005	Constipation	0.42 (0.3-0.5)
	Panzuto 2003	Constipation in previous 3 mths	16 (10-23)
Other	Flashman 2004	CBH & no RB for 6 wks >60 yrs, pts under 2WW referral	6.1 (3.8-9.6)
	Hamilton 2005	diarrhea and constipation	1.1 (0.6-1.8)
	Hamilton 2005	Diarrhea reported twice	1.5 (1.0-2.2)
	Hamilton 2005	Constipation reported twice	0.81 (0.5-1.3)
By Age/Gender	Lawrenson 2005	CBH men aged 40-49*	0.89
	Lawrenson 2005	CBH men aged 50-59*	4.07
	Lawrenson 2005	CBH men aged 60-69*	6.89
	Lawrenson 2005	CBH men aged 70-79*	8.48
	Lawrenson 2005	CBH men aged 80-89*	7.73
	Lawrenson 2005	CBH women aged 40-49*	0.64
	Lawrenson 2005	CBH women aged 50-59*	1.64
	Lawrenson 2005	CBH women aged 60-69*	2.42
	Lawrenson 2005	CBH women aged 70-79*	3.25
	Lawrenson 2005	CBH women aged 80-89*	4.09

Abbreviations: CI = confidence intervals; mth(s) = month(s); pts = patients; PPV = positive-predictive value; 2WW = two-week wait; wks = weeks; yrs = years

*Diagnosed within 12 mths of initial change in bowel habits per 100 pts presenting (men & women)

Appendix 6. Rectal bleeding (RB) and change in bowel habits (CBH).

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
RB & CBH	Chohan 2005	CBH & any RB, pts under 2WW referral	19 (14-26)
	Ellis 2005	RB & CBH	9.2 (5.2-16)
	Ellis 2005	RB & no CBH	0
	Ellis 2005	RB & CBH (loose &/or frequent)	12 (6.6-21)
	Ellis 2005	RB & CBH (hard &/or frequent)	2.8 (0.4-17)
	Ellis 2005	RB & CBH & abdominal pain	9.0 (4.1-19)
	Ellis 2005	RB & CBH & no abdominal pain	9.6 (4.1-21)
	Fijten 1995	RB & CBH (loose &/or frequent)	9.0 (4.3-18)
	Flashman 2004	RB & CBH (loose &/or frequent) for 6 wks, pts under 2WW referral	13.9 (9.7-19)
	Hamilton 2005	RB and constipation	2.4 (1.4-4.4)
	Hamilton 2005	RB and Diarrhea	3.4 (2.1-6.0)
	Mant 1989	RB & CBH; Within 3 mths	11 (4.9-22)
	Mant 1989	RB & Feeling of incomplete evacuation of rectum	12 (5.0-26)
	Metcalf 1996	RB & CBH	10 (3.9-24)
	Metcalf 1996	RB & diarrhea	7.4 (1.9-25)
	Metcalf 1996	RB & constipation	2.6 (0.4-16)
	Norrelund 1996	RB & CBH	27 (19-36)
	Robertson 2006	RB & increased frequency/loose motions	4.8 (2.8-8.1)
By Age	Norrelund 1996	>69 yrs & RB & CBH	41 (28-56)

Abbreviations: CI = confidence intervals; mth = month; pts = patients; PPV = positive-predictive value; 2WW = two-week wait; wks = weeks; yrs = years.

Appendix 7a. Anemia or iron-deficiency anemia (IDA) as single signs.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Anemia	Hamilton 2005	Low Hb 100-130 g/L	0.97 (0.8-1.3)
	Hamilton 2005	Low Hb <100 g/L	2.3 (1.6-3.1)
	Hamilton 2008	Hb 100-129 g/L	0.3 (0.2-0.3)
	Hamilton 2008	Hb <99 g/L	2.0 (1.7-2.3)
IDA	Barwick 2004	IDA Hb <100g/L, pts under 2WW referral	11
	Chohan 2005	IDA Hb <100g/L, pts under 2WW referral	34 (21-50)
	Flashman 2004	IDA: Hb ≤110 g/L for males, ≤100 g/L for females >50 yrs, pts under 2WW referral	10.9 (5.0-22)
	Panzuto 2003	IDA: Hb <140 g/L for males, <120 g/L for females, ferritin <30 µg/L and MCV <80 fl	41 (30-52)
	Stellon 1997	IDA: Hb <120 g/L and/or MCV <80 fl and ferritin ≤ 16 ng/L	7.7 (1.9-26)
	Yates 2004	IDA: >20 yrs male or >50 yrs female; Hb ≤120 g/L for males, ≤110 g/L for females; MCV <82 fl or <78 fl; red cell count <5.5 x 10^{12}/L	8.6 (6.3-12)
Anaemia by Age/Gender	Hamilton 2008	age 60-69, anemia: Hb <110 g/L for men	1.4 (0.9-2.3)
	Hamilton 2008	age 60-69, anemia: Hb <100g/L for women	1.2 (0.7-2.0)
	Lawrenson 2005	Anemia men aged 40-49*	1.07
	Lawrenson 2005	Anemia men aged 50-59*	1.86
	Lawrenson 2005	Anemia men aged 60-69*	3.02
	Lawrenson 2005	Anemia men aged 70-79*	3.38
	Lawrenson 2005	Anemia men aged 80-89*	2.98
	Lawrenson 2005	Anemia women aged 40-49*	0.08
	Lawrenson 2005	Anemia women aged 50-59*	0.56
	Lawrenson 2005	Anemia women aged 60-69*	1.38
	Lawrenson 2005	Anemia women aged 70-79*	1.99
	Lawrenson 2005	Anemia women aged 80-89*	2.01
IDA by Age/Gender	Hamilton 2008	age 60-69, IDA Hb <110 g/L for men MVC <80.0 fl or ferritin <20 ng/ml	6.5 (2.0-19)
	Hamilton 2008	age 60-69, IDA, Hb <100 g/L for women MVC <80.0 fl or ferritin <20 ng/ml	2.4 (1.0-5.7)
	Hamilton 2008	>60 yrs, IDA ; Hb <110g/L for men MVC <80.0 fl or ferritin <20 ng/ml	13.3 (9.7-18)
	Hamilton 2008	>60 yrs, IDA ; Hb <100g/L for women MVC <80.0 fl or ferritin <20 ng/ml	7.7 (5.7-11)

Abbreviations: CI = confidence intervals; fl = fluid ounce; g = grams; Hb = haemoglobin; L = litre; MCV = mean corpuscular volume; µg = microgram; mth(s) = month(s); ng = nanograms; pts = patients; PPV = positive-predictive value; 2WW = two-week wait; wks = weeks; yrs = years.
*Diagnosed within 12 mths of initial anaemia per 100 patients presenting (men & women).

Appendix 7b. Anemia or iron-deficiency anemia (IDA) as single signs.

Hamilton 2008	Sign & Gender	Age group	Hb levels (g/dL) (95% CI)					
			<90	90-99	100-109	110-119	120-129	≥130
Hamilton 2008	Anemia men	30-59 yrs	1.3 (0.4-4.3)	1.4 (0.2-10)	0.8 (0.3-2.2)	0.8 (0.2-2.9)	0.2 (0.1-0.3	0.1 (0.1-0.1)
Hamilton 2008	Anemia men	60-69 yrs	7.6 (3.4-16)	7.2 (2.9-17)	2.3 (1.1-4.8)	1.4 (0.9-2.3)	0.7 (0.5-1.0)	0.3 (0.3-0.3)
Hamilton 2008	Anemia men	70-79 yrs	8.8 (5.4-14)	4.0 (2.5-6.3)	3.2 (2.2-4.8)	1.5 (1.2-2.0)	1.0 (0.7-1.2)	0.4 (0.3-0.4)
Hamilton 2008	Anemia men	≥ 80 yrs	6.8 (4.2-11)	6.0 (3.4-10)	1.6 (1.1-2.2)	1.0 (0.8-1.4)	0.6 (0.5-0.8)	0.4 (0.3-0.5)
Hamilton 2008	Anemia women	30-59 yrs	0.9 (0.3-2.9)	0.3 (0.1-0.6	0.4 (0.2-0.8)	0.1 (0.1-0.2)	0.0 (0.0-0.1)	0.0 (0.0-0.0)
Hamilton 2008	Anemia women	60-69 yrs	>5	2.7 (1.2-5.9)	1.2 (0.7-2.0)	0.4 (0.3-0.6)	0.2 (0.1-0.2)	0.1 (0.1-0.2)
Hamilton 2008	Anemia women	70-79 yrs	8.6 (5.4-14)	3.6 (2.1-6.0)	1.9 (1.4-2.6)	0.5 (0.4-0.6)	0.3 (0.3-0.4)	0.2 (0.2-0.2)
Hamilton 2008	Anemia women	≥ 80 yrs	7.1 (4.5-11)	2.2 (1.5-3.1)	1.2 (0.9-1.5)	0.6 (0.5-0.8)	0.3 (0.2-0.4)	0.2 (0.2-0.3)
Hamilton 2008	IDA men	60-69 yrs	>5	12 (3.1-37)	5.5 (1.2-21)	6.5 (2.0-19)	1.8 (0.7-4.2)	1.4 (0.6-3.6)
Hamilton 2008	IDA men	70-79 yrs	18 (8.7-34)	16 (6.3-35)	14 (5.9-29)	4.1 (2.1-8.0)	3.9 (1.8-8.5)	1.7 (0.9-3.1)
Hamilton 2008	IDA men	≥ 80 yrs	15 (7.3-28)	31 (5.6-77)	8.2 (3.7-17)	4.0 (1.6-9.3)	1.5 (0.5-4.2)	1.4 (0.6-3.1)
Hamilton 2008	IDA women	30-59 yrs	0.6 (0.2-2.2)	0.3 (0.1-0.8)	0.6 (0.2-2.1)	0.2 (0.1-0.4)	0.1 (0.0-0.3)	0.1 (0.0-0.3)
Hamilton 2008	IDA women	60-69 yrs	>5	3.5 (1.1-11)	2.4 (1.0-5.7)	1.5 (0.7-3.3)	0.1 (0.0-0.8)	2.9 (0.6-12)
Hamilton 2008	IDA women	70-79 yrs	10 (5.2-19)	8.6 (3.8-18)	5.9 (3.0-11)	2.1 (1.1-4.0)	0.8 (0.4-1.7)	0.4 (0.2-1.1)
Hamilton 2008	IDA women	≥ 80 yrs	10 (5.6-17)	5.7 (3.0-11)	2.5 (1.5-4.1)	3.6 (2.0-6.5)	1.5 (0.5-4.2)	0.8 (0.3-1.8)

Abbreviations: CI = confidence intervals; IDA = iron-deficiency anemia; yrs = years.

Appendix 8. Perianal symptoms, weight loss, abdominal pain and other symptoms or signs as single symptoms or signs.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Weight loss	Barwick 2004	Weight loss, pts under 2WW referral	5
	Hamilton 2005	Weight loss	1.2 (0.9-1.6)
	Hamilton 2005	Wt loss reported twice	1.4 (0.8-2.6)
	Panzuto 2003	Weight loss - Decrease >3 kg in 3 mths prior to visit	36 (23-51)
	Steine 1994	Weight loss	4.8 (3.0-7.6)
Nausea/vomiting	Steine 1994	Nausea	1.8 (1.0-3.3)
Abdominal pain	Barwick 2004	Abdominal pain, pts under 2WW referral	7
	Hamilton 2005	abdominal pain	1.1 (0.9-1.3)
	Hamilton 2005	abdominal pain reported twice	3.0 (1.8-5.2)
	Muris 1993	abdominal pain (selected pt)	0.5 (0.2-1.6)
	Panzuto 2003	Abdominal pain	13 (9.6-19)
	Steine 1994	Abdominal pain	2.1 (1.4-3.0)
Abdominal tenderness/bloating	Hamilton 2005	Abdominal tenderness	1.1 (0.8-1.5)
	Hamilton 2005	Abdominal tenderness reported twice	1.7 (0.8-3.7)
	Hamilton 2005	Abdominal tenderness and abdominal pain	1.4 (0.3-2.2)
	Panzuto 2003	bloating	13 (8.8-19)
	Steine 1994	Abdominal distension	2.6 (1.9-3.6)
Fatigue	Steine 1994	Fatigue	1.9 (1.2-2.9)

Abbreviations: CI = confidence intervals; kg = kilograms; mths = months; pts = patients; PPV = positive-predictive value; 2WW = two-week wait; wks = weeks; yrs = years.

Appendix 9. Combination of rectal bleeding (RB) and other symptoms.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Perianal symptoms	Fijten 1995	RB & perianal eczema	18 (5.8-43)
	Mant 1989	RB & anal itch	2.8 (0.4-17)
	Mant 1989	RB & anal protrusion	3.3 (0.5-20)
	Mant 1989	RB & pain on defecation	6.7 (1.7-23)
	Robertson 2006	RB & hemorrhoids	3.1 (1.7-5.7)
	Robertson 2006	RB & hemorrhoids and bright red blood not mixed with stool	1.9 (0.6-5.7)
	Robertson 2006	RB & hemorrhoids and no other symptoms except bright non-mixed bleeding	3.3 (1.1-9.8)
	Wauters 2000	RB & spasms	5.4 (2.0-11)
Abdominal Pain	Fijten 1995	RB & abdominal pain	2.2 (0.7-6.7)
	Fijten 1995	RB & pain at night	0
	Hamilton 2005	Abdominal pain and RB	3.1 (1.9-5.3)
	Mant 1989	RB & abdominal pain last 3 mths	9.3 (3.5-22)
	Metcalf 1996	RB & abdominal pain	7.1 (2.3-20)
	Norrelund 1996	RB & abdominal pain	23 (16-33)
	Robertson 2006	RB & abdominal pain	1.7 (0.6-4.5)
	Wauters 2000	RB & pain	0 (0-10)
Abdominal tenderness	Hamilton 2005	Abdominal tenderness and RB	4.5
Weight loss	Fijten 1995	RB & weight loss	9.5 (3.6-23)
	Hamilton 2005	Weight loss and RB	4.7
	Mant 1989	RB & weight loss	14 (3.6-43)
	Metcalf 1996	RB & weight loss	13 (3.4-41)
	Norrelund 1996	RB & weight loss	23 (13-37)
	Robertson 2006	RB & weight loss	4.8 (1.6-14)
	Wauters 2000	RB & Weight loss	16 (4.5-36)
Other	Fijten 1995	RB & decreased appetite	2.4 (0.3-15)
	Fijten 1995	RB & nausea	1.5 (0.2-9.7)
	Fijten 1995	RB & pale conjunctivae	17 (2.3-63)
	Fijten 1995	RB & family history of abdominal disease	0
	Mant 1989	RB & first-degree relative with CRC	10 (2.5-32)
	Metcalf 1996	RB & associated slime	11 (3.5-28)
	Wauters 2000	RB & fatigue	7.1 (8.3-16)

Abbreviations: CI = confidence intervals; mths = months; PPV = positive-predictive value; yrs = years.

Appendix 10. Combination of change in bowel habits (CBH) and other symptoms.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Abdominal pain or tenderness	Hamilton 2005	abdominal pain and constipation	1.5 (1.0-2.2)
	Hamilton 2005	abdominal tenderness and constipation	1.7 (0.9-3.4)
	Hamilton 2005	abdominal pain and diarrhea	1.9 (1.4-2.7)
	Hamilton 2005	abdominal tenderness and diarrhea	2.4 (1.3-4.8)
Weight loss	Hamilton 2005	wt loss and constipation	3.0 (1.7-5.4)
	Hamilton 2005	wt loss and diarrhea	3.1 (1.8-5.5)
Anemia	Hamilton 2005	Hb 100-130 g/L and constipation	1.2 (0.6-2.7)
	Hamilton 2005	Hb <100g/L and constipation	2.6
	Hamilton 2005	Hb 100-130 g/L and diarrhea	2.2 (1.2-4.3)
	Hamilton 2005	Hb <100 g/L and diarrhea	2.9

Abbreviations: CI = confidence intervals; g = grams; Hb = hemoglobin; L = litre; mth = month; PPV = positive-predictive value.

Appendix 11. Combination of anaemia and other symptoms.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Abdominal pain or tenderness	Hamilton 2005	Hb <100 g/L and abdominal tenderness	>10
	Hamilton 2005	Hb<100 g/L and abdominal pain	6.9
	Hamilton 2005	Hb 100-130 g/L and abdominal tenderness	2.7
	Hamilton 2005	Hb 100-130 g/L and abdominal pain	2.2 (1.1-4.5)
Weight loss	Hamilton 2005	Hb <100 g/L and weight loss	4.7
	Hamilton 2005	Hb 100-130 g/L and weight loss	1.3 (0.7-2.6)
Rectal bleeding	Hamilton 2005	Hb <100 g/L and RB	3.2
	Hamilton 2005	Hb 100-130 g/L and RB	3.6

Abbreviations: CI = confidence intervals; g = grams; Hb = hemoglobin; L = litre; PPV = positive-predictive value; RB = rectal bleeding.

Appendix 12. Combination of other symptoms.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Various	Hamilton 2005	abdominal pain and weight loss	3.4 (2.1-6.0)
	Hamilton 2005	abdominal tenderness and weight loss	6.4
	Hamilton 2005	abdominal tenderness and abdominal pain	1.4 (0.3-2.2)

Abbreviations: CI = confidence intervals; PPV = positive-predictive value.

Appendix 13. Abdominal or rectal mass.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Abdominal mass	Chohan 2005	abdominal mass; 2WW referral	41 (21-65)
	Flashman 2004	Right-sided abdominal mass; 2WW referral	16.3 (8.0-30)
Rectal mass	Chohan 2005	rectal mass; 2WW referral	80 (57-92)
	Flashman 2004	rectal mass; 2WW referral	22.6 (13-36)
Abdominal or rectal mass	Barwick 2004	abdominal or rectal mass; 2WW referral	16.7

Abbreviations: CI = confidence intervals; PPV = positive predictive value; 2WW = two-week wait.

Appendix 14. Multiple regression.

Study	Included in model	Significant predictors	Level of significance
Fijten 1995	Blood seen mixed with stool only, blood seen on stool or mixed with only, blood seen – others or combinations, Blood seen – unknown, abdominal pain, change in bowel habit (loose &/or frequent), pain at night, decreased appetite, nausea, weight loss, family history of abdominal disease, previous history of rectal bleeding, pale conjunctivae, perianal eczema, rectal palpation (hemorrhoid), rectal palpation (tumour), rectal palpation (abnormal prostate), proctoscopy abnormal, age, gender	Age, change in bowel habit, blood mixed with stool or on stool	p<0.05
Hamilton 2008	Hb stratified into 6 bands: <9, 9, 10, 11, 12, 13 g/dL, age stratified into 4 bands: 30-59, 60-69, 70-79, 80+, microcytosis <80.0 fL, low ferritin <20 ng/mL	Anemia, microcytosis, low ferritin, antagonistic interaction between microcytosis and low ferritin	p<0.001
Hamilton 2005	Included 56 variables in model, only reported some of the variables: Rectal bleeding, loss of weight, number of episodes of abdominal pain, constipation, number of episodes of diarrhea, rectal disease on rectal examination, tenderness on palpation of abdomen, FOBT+, low hemoglobin category, no low hemoglobin, haemoglobin 12.0–12.9 g/dL, haemoglobin 10.0–11.9 g/dL, haemoglobin <10 g/dL, blood sugar >10 mmol/L, age, gender	These were reported: Rectal bleeding, loss of weight, number of episodes of abdominal pain, constipation, number of episodes of diarrhea, rectal disease on rectal examination, tenderness on palpation of abdomen, positive faecal occult blood, low hemoglobin category, blood sugar >10 mmol/L, age; antagonistic interactions: hemoglobin subcategory with age group, abdominal pain with tenderness, FOBT+ with hemoglobin <10 g/dL	p<0.05
Norrelund 1996	Gender, age, patient thought bleeding due to cancer, weight loss, abdominal pain, change in bowel habits, discomfort, rectal bleeding	Age, change in bowel habits	p<0.05
Panzuto 2003	Age >50 yrs, weight loss, IDA	Age >50 yrs, IDA	p<0.05
Park 2009	Age, sex, lifestyle factors (BMI, waist-to-hip ratio, smoking status, energy intake, alcohol intake, dietary fibre intake, meat intake), bowel movement (frequency, consistency, quantity, discomfort), laxative use	Loose vs. soft stools (adjusted for age and sex, or lifestyle factors or age, sex, lifestyle factors, bowel movement and laxative use)	p=0.003
Parker 2007	Age, sex, area deprivation level, BMI, smoking status, blood pressure, comorbidities	Age, sex, smoking status, coronary heart disease (each variable was adjusted for all other variables in model)	p<0.05
Robertson 2006	Age group, sex, dark blood, blood mixed in stool, increased or looser stools, patient reported IBS	Age, blood mixed in stool	p<0.05

Steine 1994	Age group, sex, family history of cancer, previous CRC/polyps, rectal bleeding, loss of weight, abdominal pain, fatigue, abdominal distension, nausea	Age, sex, rectal bleeding, loss of weight	p<0.05

Abbreviations: BMI = body mass index; CRC = colorectal cancer; dL = decalitre; fL = femtolire; FOBT = fecal occult blood test; g = grams; Hb = hemoglobin; IBS = irritable bowel syndrome; IDA = iron-deficiency anemia; L = litre; mmol = millimoles; ng,= nanograms; yrs = years.

Appendix 15. Summary of pooled diagnostic measures from meta-analyses.

Index test	Author	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)	Pooled PPV % (95% CI)	Pooled positive-likelihood ratio (95% CI)
RB	Astin 2011			8.1 (6.0-10.8)	
	Ford 2008	64 (55-73)	52 (42-63)		1.32 (1.19-1.47)
	Jellema 2010	44	66	7 (5-10)	
	Shapley 2010			4.57 (3.68-5.46)	
Dark RB	Ford 2008	15 (3-34)	96 (93-98)		3.83 (2.62-5.61)
	Jellema 2010	35	85	14 (9-21)	
	Olde Bekkink 2010	22 (13-34)	84 (69-93)		1.37 (0.59-3.30)
RB mixed with stool	Jellema 2010	51	71	6 (4-10)	
	Olde Bekkink 2010	40 (4-93)	81 (23-98)		1.91 (0.75-5.51)
Previous history of RB	Olde Bekkink 2010	30 (5-41)	66 (63-71)		0.58 (0.14-1.41)
RB & age ≥70	Shapley 2010			5.54 (3.91-7.17)	
RB & abdominal pain	Astin 2011	33 (24.0-42.5)	63 (60.1-65.3)	7.58 (3.00-19.2)	1.03 (0.63-1.69)
RB & weight loss	Astin 2011	19 (12.3-27.9)	89 (86.7-90.2)	13.4 (8.15-21.9)	1.88 (1.25-2.83)
RB & CBH	Astin 2011	58 (49.0-67.3)	63 (60.4-65.1)	11.8 (6.78-20.4)	1.81 (1.33-2.46)
CBH	Ford 2008	41 (23-60)	69 (58-78)		1.29 (1.05-1.59)
	Jellema 2010	52	61	9	
	Olde Bekkink 2010	62 (18-94)	68 (53-80)		1.92 (0.54-3.57)
Diarrhea	Ford 2008	19 (1-54)	80 (63-93)		0.74 (0.34-1.62)
	Jellema 2010	20 (14-29)	73 (67-78)	6 (2-15)	
Constipation	Jellema 2010	13	72	6 (2-18)	
Anemia	Astin 2011			9.70 (3.52-26.8)	
	Ford 2008	17 (5.5-33)	90 (87-92)		1.43 (0.75-2.74)
	Olde Bekkink 2010	17 (5-35)	95 (93-96)		3.67 (1.30-10.35)
Iron-deficiency anemia	Ford 2008	23 (2-57)	87 (83-91)		1.38 (0.48-3.94)
	Jellema 2010	13	92	13	
Weight loss	Ford 2008	22 (14-31)	89 (81-95)		1.96 (1.25-3.08)
	Jellema 2010	20	89	9	
	Olde Bekkink 2010	17 (6-37)	91 (83-96)		1.89 (1.03-3.07)
Pain on defecation	Olde Bekkink 2010	22 (13-36)	41 (22-78)		0.49 (0.25-0.97)
Itch/eczema	Olde Bekkink 2010	17 (7-33)	81 (73-95)		1.31 (0.25-6.21)
Hemorrhoid	Olde Bekkink 2010	24 (9-45)	73 (46-91)		0.51 (0.09-2.97)
Abdominal pain	Astin 2011			3.29 (0.69-15.6)	
	Jellema 2010	35	59	5	
	Olde Bekkink 2010	25 (4-62)	73 (52-89)		0.94 (0.19-1.59)

Index test	Author	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)	Pooled PPV % (95% CI)	Pooled positive-likelihood ratio (95% CI)
Abdominal mass	Ford 2008	5 (2-9)	97 (96-98)		1.47 (0.68-3.19)
Age <40	Olde Bekkink 2010	3 (0-16)	73 (69-76)		0.32 (0.05-2.21)
Age 40-59	Olde Bekkink 2010	9 (4-19)	79 (70-86)		0.41 (0.18-0.90)
Age ≥60	Olde Bekkink 2010	66 (45-83)	76 (68-83)		2.79 (2.00-3.90)
Age >50 v <50	Jellema 2010	91	36	10 (7-13)	
Age >60 v <60	Jellema 2010	83	55	9 (8-10)	
Age >70 v <70	Jellema 2010	50	79	13	
Male	Jellema 2010	62	55	7 (5-12)	
	Olde Bekkink 2010	58 (48-67)	52 (48-56)		1.21 (1.00-1.46)
Family history	Jellema 2010	16	91	6	
	Olde Bekkink 2010	15 (6-28)	85 (82-87)		1.05 (0.16-6.88)
FOBT (guaiac)	Jellema 2010	75	86	28	
FOBT (immunochemical)	Jellema 2010	95	84	21	

Abbreviations: CBH = change in bowel habits; CI = confidence intervals; FOBT = fecal occult blood test; PPV = positive-predictive value; RB = rectal bleeding.

Appendix 16. Diagnostic investigations.

Author	Test	PPV (95% CI)	Other parameters (95% CI)
Bjerregaard 2009	Hemoccult Sensa® FOBT	10.5 (6.8-14.3)	SE=75 (69.7-80.3); SP=79.4 (74.5-84.4); NPV=99 (97.8-100)
McSherry1969	FOBT+; in 1228 patients		SE=73.3
Oono 2010	Immunochemical FOBT	33.7 (27.5-40.5)	SE=74.7 (64.8-82.6); SP=86.4 (84.1-83.4); NPV=97.4 (96.1-98.2); POS LR=5.48 (4.49-6.67); NEG LR=0.29 (0.21-0.42); OR=18.7 (11.3-31.1)
Shaw 2008	Hemoccult® FOBT	7.7 (1.9-26)	
Viiala 2007	FOBT+	14.3	OR=5.9 (1.2-29.7)
Fijten 1995	RB & rectal palpation (hemorrhoid)	10 (2.5-32)	SE=22; SP=93; NPV=97; OR=3.8
Fijten 1995	RB & rectal palpation (abnormal prostate)	50 (5.9-94)	SE=11; SP=99.6; NPV=97; OR=31.8
Fijten 1995	RB & rectal palpation (tumour)	100	SE=11; SP=89; NPV=97; OR=undefined
Fijten 1995	RB & proctoscopy abnormal	0	SE=0; SP=30; NPV=87; OR=0.2
Fijten 1995	RB & Hb low (female < 7.5 mmol/L, male <8.5 mmol/L)	14 (3.6-43)	SE=33; SP=95; NPV=98; OR=8.8
Fijten 1995	RB & ESR high (female >28 mm/h, male >12 mm/h)	8.7 (2.2-29)	SE=40; SP=91; NPV=98; OR=6.3
Fijten 1995	RB & ESR high >30 mm/h	17 (4.2-48)	SE=40; SP=96; NPV=99; OR=14
Fijten 1995	RB & White blood cell count high $>10^9$/L	12 (3.9-31)	SE=75; SP=90; NPV=99.5; OR=26.3
Hamilton 2005	Abnormal rectal exam	1.5 (1.0-2.2)	
Hamilton 2005	Abnormal rectal exam and RB	8.5	
Hamilton 2005	Abnormal rectal exam and constipation	2.6	
Hamilton 2005	Abnormal rectal exam and diarrhea	11	
Hamilton 2005	Abnormal rectal exam and abdominal pain	3.3	
Hamilton 2005	Abnormal rectal exam and abdominal tenderness	5.8	

Author	Test	PPV (95% CI)	Other parameters (95% CI)
Hamilton 2005	Abnormal rectal exam and wt loss	7.4	
Mant 1989	RB & hemorrhoids identified by FP	5.4 (2.0-14) p<0.05	SE=25 (10-51); SP=46 (37-54); POS LR=0.46 (0.19-1.09); NEG LR=1.64 (1.17-2.30); NPV=83 (73-90); OR=0.28 (0.09-0.92)
Wauters 2000	RB & palpable tumour	32 (13-57)	
Chen 2006	Ultrasonography	95 (88-98)	SE=93 (86-97); SP=99 (97-99); POS LR=76.8 (32.1-184); NEG LR=0.07 (0.04-0.15); NPV=98 (97-99); OR=1051 (326-3389)
Martinez-Ares 2005	Abdominal ultrasound	81 (66-90)	SE=79 (64-89); SP=92 (85-96); POS LR=10.1 (5.09-20); NEG LR=0.23 (0.13-0.41); NPV=91 (84-95); OR=44.4 (15.8-124) adjusted OR= 9.26 (4.8-17.5); Regression=P<0.05
Martinez-Ares 2009	Abdominal ultrasound	78.5	SE=83.3; SP=82.7; NPV=86.7; accuracy=83
Duff 2006	CT colonography	70 (38-90)	SE=88 (46-98); SP=97 (91-99); POS LR=30.3 (9.65-95.4); NEG LR=0.13 (0.02-0.81); NPV=99 (93-99.8); OR=236 (21.6-2570)
Roberts-Thomson 2008	CT colonography	63 (28-87)	SE=56 (25-82); SP=98 (95-99); POS LR=35.7 (10.1-127); NEG LR=0.45 (0.22-0.94); NPV=98 (95-99); OR=79.2 (13.9-451)
Robinson 2011	CT colonography		SE=93.6
Sofic 2010	CT colonography	100	SE=100; SP=100
Taylor 2003	CT colonography		SE=83
Tolan 2007	CT colonography		SE=93 (77-98)
White 2009	CT colonography		SE=100; SP=99.2
Koo 2005	Minimal-preparation computed tomography		SE=Pooled 83 (76-88); SP=Pooled 90 (85-94)
Brewster 1994	FS		SE=52 (32-72)
Thompson 2008	FS		SE=99 (98-99)
Irvine 1988	FS		SE=67
Anderson 2011	RS		Diagnostic accuracy of surgical assessment for CRC significantly better than general practitioner assessment due to surgeons' use of RS
Helfand 1997	RS		SE=77 (48-92)
Helfand 1997	RS & DCBE		SE=100
Jensen 1993	Rectosigmoidoscopy		SE=40
Irvine 1988	FS & DCBE		SE=83
Rex 1990	FS & ACBE		Chi-squared NS p>0.05
Anderson 1991	SCBE or DCBE		SE=71
Brewster 1994	DCBE		SE=100
Helfand 1997	DCBE		SE=92 (61-99)
Irvine 1988	DCBE		SE=83
Jensen 1993	DCBE		SE=60

Author	Test	PPV (95% CI)	Other parameters (95% CI)
Sofic 2010	Barium enema	100	SE=94.6; SP=100
Tate 1988	FP-referred DCBE		Diagnostic yield=3
Thompson 2008	DCBE		SE=86 (78-92)
Church 1991	Air-contrast barium enema	71 (56-83)	SE=75 (59-86); SP=43 (24-64); Pos LR=1.31 (0.87-1.98); Neg LR=0.58 (0.28-1.21); NPV=47 (27-69); OR=2.25 (0.73-6.91)
Ott 1989	Single- or double-contrast barium enema		SE=100

Abbreviations: CBH = change in bowel habits; CI = confidence intervals; CT = computed tomography; DCBE = double-contrast barium enema; ESR = erythrocyte sedimentation rate; FS = flexible sigmoidoscopy; FOBT = fecal occult blood test; FP = family physician; h = hour; Hb = haemoglobin; L = litre; LR = likelihood ratio; mm = millimetre; mmol = millimoles; Neg = negative; NPV = negative-predictive value; OR = odds ratio; Pos = positive; PPV = positive-predictive value; RB = rectal bleeding; RS = rigid sigmoidoscopy; SCBE = single-contrast barium enema; SE = sensitivity; SP = specificity.

Appendix 17. Personal or family history as single risk factors.

Index test	Author	Definition of sign/symptom	PPV (%)(95% CI)
Personal history	Steine 1994	Personal history of CRC/polyp	5.7 (2.6-12)
Family history	Steine 1994	Family history of CRC/polyp	1.3 (0.4-3.9)

Abbreviations: CI = confidence intervals; CRC= colorectal cancer; PPV= positive-predictive value.

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Evidence-Based Series 24-1: Section 3 - Development Methods, Recommendations Development and External Review Process

Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers: EBS Development Methods and External Review Process

L. Del Giudice, E. Vella, A. Hey, W. Harris, M. Simunovic, C. Levitt, and the Colorectal Cancer Referral Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 24, 2012

The 2012 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Below are the original methods and review from 2012. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2009 and 2015 and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an

interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Provincial Primary Care and Cancer Network of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on primary care referral for suspected colorectal cancer, developed through the review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Development of the Recommendations for Referral

Estimated positive-predictive values (PPVs) of each possible sign and symptom of CRC were extracted from the peer-reviewed literature. The recommendations for urgency of referral associated with the PPV of each sign and symptom were aligned with the same relative urgency as a positive FOBT in Ontario's CRC screening program, ColonCancerCheck (3). The PPV for the detection of CRC using Hema Screen, the FOBT used in the Ontario ColonCancerCheck screening program, in single (one-time) testing of asymptomatic adults was estimated to be 10.9% (4). Therefore, the Colorectal Cancer Referral Working Group believed that signs or symptoms with PPVs greater than 10% should lead to a higher index of suspicion of CRC and more urgent referral.

The Working Group agreed that the urgency of referral for signs and/or symptoms of CRC should be comparable to current published Canadian guidelines by Paterson et al (2006) (5). Where not available, the urgency of referral was based on comparable PPVs for CRC of established target wait times: in particular, the target wait time of eight weeks for colonoscopy for a positive FOBT from the ColonCancerCheck Program in Ontario (3).

The signs and symptoms leading to referral demonstrated PPVs of 10% or greater. The term 'unexplained' was used to emphasize that clinical judgement is necessary to rule out other possible causes for rectal bleeding or IDA. The cutoff value for hemoglobin to assess anemia was taken from the two-week referral guideline developed by the National Institute for Health and Clinical Excellence (NICE) in 2005 and endorsed by the New Zealand Guidelines Group (NZGG) in 2009 (6,7). Although median PPVs were not calculated for rectal or abdominal masses because there were less than four studies found for each sign, the Working Group chose

to include these signs to prompt referrals because all PPVs for each study were over 10% and because of their own clinical experience with these signs.

Expert Panel Review

Key issues raised by the guideline Expert Panel and the Working Group responses (italicized) included the following:

- Change the title to "Referral of Patient with Suspected Colorectal Cancer by Primary Care Practitioners"
  - *The title was changed.*
- The guideline does address symptomatic people with a strong family history?
  - *Under Target Population, the sentence "These recommendations are not intended to provide recommendations for patients who should be in a surveillance program such as those with inflammatory bowel disease, a personal history of CRC, or patients with a strong family history of CRC." was changed to "Patients at increased risk of CRC such as a personal history of CRC, inflammatory bowel disease or a first-degree family member with CRC should be in a CRC surveillance program involving regular colonoscopies. Clinical judgement about the need for referral should be exercised if these patients present with interim new or worsening symptoms."*
- I don't think I like the suggestion "be vigilant" in a guideline – it's something that we always have to do, kind of like "develop a differential diagnosis" or "be caring."
  - *Under Target Population, the sentence "Ongoing vigilance during the diagnostic assessment by the primary care provider can be expected to minimize the impact of unexpected situations such as missed or inaccurate diagnostic tests." was changed to "During the process of referral and the diagnostic assessment pathway, FPs and other PCPs should apply the College of Physicians and Surgeons of Ontario's policy on Test Results Management to ensure that an appropriate response to test results are met (8)."*
- A focused physical exam *could* include the following manoeuvres" would seem like more appropriate wording, to me.
  - *The recommendation "A focused physical examination should at the very least include the following manoeuvres; as their sole or combined presence and/or absence can inform the primary care provider." was changed to "To supplement the history, a focused physical examination could include the following manoeuvres:"*
- Digital rectal exam and/or proctoscopy: this implies proctoscopy alone is OK.
  - *The recommendation "Digital rectal examination and/or proctoscopy" was changed to "Digital rectal examination followed by proctoscopy if indicated and available"*
- "The following tests may be helpful to complete the assessment..." urine test for blood is included. Later on you say the urine test is needed if there is anemia, to rule out a urinary tract cause of anemia. It seems that this recommendation should be clarified. That is, if there is no anemia, a urinary test for blood isn't required.
  - *The recommendation "Urine test for blood" was removed because positive results would not increase the urgency of referral.*
- I see why this (FOBT) is included due the Jellema meta-analysis yet when I have participated in CIRT calls I've often heard that we should not be seeing FOBT testing for symptomatic patients (9). On page 14, it explains in clearer detail that FOBT testing is recommended as an interim test while the patient is waiting for colonoscopy so this is something that may need to be added to the CIRT decision tree? I also think it may be good in this section to be more explicit in the reason for an FOBT test in a symptomatic patient (as an interim test) as explained clearly on pg 15: 'Since IDA or rectal bleeding

mixed with stool have PPV values greater than 10%, and FOBTs showed good diagnostic performance for CRC among symptomatic patients (9), a complete blood count and FOBT can be ordered but should not delay referral. The results of these tests should be made available to specialists to help them prioritize patients.'
    - *The recommendation "The following tests* may be helpful to complete the assessment but should not delay referral" was changed to "The following may be helpful ancillary tests* but their completion should not delay referral". Also, "Positive results may increase the urgency of referral." was added.*
- I strongly disagree with FOBT as a diagnostic test. Although a positive test may encourage one to speed the referral, a negative test might harm the process by relaxing time for appropriate workup. There is a high risk of a negative FOBT delaying referral in my opinion.
    - *See previous response.*
- Patients should expect to see their primary care provider within 1 week of the initial phone call, when they complain of any symptom that could suggest CRC. (you're letting primary care get off way too easy by only emphasizing time from referral to consultation, the true wait time is time from the initial phone call. What's the point of a 2 week referral guideline if it takes 8 weeks to see the GP? There is some evidence that primary care waits correlate with worse mortality, and that open access scheduling improves primary care capacity, diagnosis of new conditions, and improved chronic disease management.
    - *This recommendation was added to the delay section "FPs and other PCPs should consider implementing systems (e.g., open-access booking) to expedite initial appointments for patients calling with signs and/or symptoms suggestive of CRC."*
- Under referral section: will there be a reference here to any DAP's if available in your Region as should be upcoming? not necessarily as part of the CCC but in alignment with that program
    - *The DAP was added to the recommendations as a source for referral.*
- My main concern within the recommendations, if I understand them correctly, is the suggestion that in the event that there is a delay in the workup of a patient with a likely colorectal cancer, that tests with unacceptable false-negative results (DCBE, CT colonography, sigmoidoscopy) be performed while awaiting a definitive colonoscopy. I'm not certain of the value in performing these tests (which have unacceptable false-negative results) as a positive or negative test will not alter the ultimate investigations required by the patient but only expose the patient to additional procedures and risks at additional costs, and may in fact delay the definitive investigations. How do these tests make excess wait times any less of a problem? If negative or positive, the same work up will be done by the specialist.
    - *The statement "Normal or negative results should not lead to a cancellation of the consult with the CRC DAP or specialist. Positive results may facilitate more timely investigation of a patient" was added.*
- Recommendations to Reduce Diagnostic Delay (I think, in this section, you should say something about endoscopists developing appropriate triage protocols)
    - *The recommendation "CRC DAPs and specialists competent in endoscopy should develop triage protocols to avoid delays in the diagnosis of CRC in patients with suspicious signs and/or symptoms." was added.*
- During the periodic or annual health exam, primary care providers, should at minimum, ask patients about rectal bleeding and about change in bowel habits and family history of CRC

- *The recommendation "During the periodic or annual health examination, primary care providers, should at minimum, ask patients about rectal bleeding and about change in bowel habits." was changed to "During the periodic health examination, FPs and other PCPs, should at a minimum, ask patients who are 50 years or older about rectal bleeding, about change in bowel habits, and about a family history for CRC." Annual health examinations were deleted to promote periodic health examinations instead. An age of 50 and older was included to mirror the risk assessment approach for CRC screening in Ontario for average-risk, asymptomatic patients.*

Internal Review: PEBC Director

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the Director of the PEBC, Dr. Melissa Brouwers, with expertise in methodological issues. The key issues raised by the Director and the Working Group responses (italicized) were the following:

- In the recommendations, it states with some of the investigations, if the investigation comes up negative but do not let that outcome delay referral. What is their purpose then? If it will not differentiate course of action it is very unclear why one would recommend them. Similarly, there are two procedures recommended in the case of a long delay – what are their purposes? A justification is required.
  - *A justification is presented under Key Evidence.*
- I think a summary at the end of each question would be helpful.
  - *A summary is included at the end of each question.*
- Most of the investigations data focus on PPV, NPV, sensitivity and specificity data – there is nothing about risks of the procedures. Are these data not available or were not searched? That might be worth a point in the discussion.
  - *This is addressed in the Discussion.*
- A bit more interpretation of the data (rather than a summary of the evidence) in the discussion would useful - for example, first and third points could be addressed there.
  - *The first and third points are addressed in the Discussion.*

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC's Director, the Colorectal Cancer Referral Working Group circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Colorectal Cancer Referral Working Group.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review June 20, 2011)

QUESTIONS
Overall Question

In patients presenting to family physicians (FPs) and other primary care providers (PCPs) with signs and/or symptoms of colorectal cancer (CRC), what should

the referral process include? The following questions are the factors considered in answering the overall question:

1. What signs, symptoms, and other clinical features are predictive of CRC?
2. What is the diagnostic accuracy of investigations for CRC?
3. What major, known risk factors are predictive of CRC?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers?
5. Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION

Patients at average risk for CRC presenting in primary care settings comprise the target population. Patients at increased risk of CRC such as those with a personal history of CRC, inflammatory bowel disease or a first-degree family member with CRC should be in a CRC surveillance program involving regular colonoscopies. Clinical judgement about the need for referral should be exercised if these patients present with interim new or worsening symptoms. In addition, this guideline does not provide recommendations for patients who present with emergency alarm features such as anemia resulting in symptoms and signs of hemodynamic instability, acute gastrointestinal hemorrhaging, acute intestinal obstructions, or unremitting abdominal pain. These patients should be referred for emergency assessment. During the process of referral and along the diagnostic assessment pathway, FPs and other PCPs should apply the College of Physicians and Surgeons of Ontario's policy on Test Results Management to ensure that an appropriate response to test results are met (1).

INTENDED USERS

This guideline is targeted to FPs, general practitioners, emergency room physicians, other PCPs (nurse practitioners, registered nurses, and physician assistants), surgeons and gastroenterologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as 'FPs and other PCPs'.

RECOMMENDATIONS

Clinical Presentation
A focused history and physical examination should be performed if patients present with one or more of the following signs or symptoms that could inform the FPs and other PCPs in the diagnosis of CRC: • Palpable rectal mass • Palpable abdominal mass • Anemia (especially iron-deficiency anemia [IDA]) • Rectal bleeding • Change in bowel habits • Weight loss • Abdominal discomfort • Perianal symptoms
The focused history should determine the following details: • Age and gender • Rectal bleeding, and if yes,

- Colour (dark versus bright red)
- Location of blood relative to stool (mixed in with stool versus separate from stool, on the toilet paper)

- Change in bowel habit over recent months/years, and if yes,
  - Increased loose or watery stools or diarrhea
  - Increased constipation or difficulty passing stools
  - Feeling of incomplete emptying
  - Increased urgency
  - Incontinence of stools or soiling
- Weight loss
- Abdominal discomfort (pain, tenderness, bloating)
- Perianal symptoms such as prolapsed lump, pruritus, pain, hemorrhoids
- Family history of first-degree relative and the age of onset
- Symptoms of anemia (fatigue, weakness, dyspnea on exertion/poor exercise tolerance, palpitations/tachycardia, dizziness, anorexia, headache, and/or cold intolerance)
- History of unexplained IDA
  - If the patient's presenting sign (complaint) is unexplained anemia or IDA, the patient's history should also include questions about diet, prescribed and non-prescribed medications (especially non-steroidal anti-inflammatory drugs [NSAIDs]), menstrual history, frank bleeding (injury or epistaxis), recent surgery, blood donation, and a personal or family history of a blood disorder.

To supplement the history, a focused physical examination could include the following manoeuvres:

- Digital rectal examination (DRE) followed by proctoscopy if indicated and available
- Abdominal examination
  - Signs of anemia such as skin and/or conjunctival pallor, loss of skin tone, tachycardia, increased pulse pressure, systolic ejection murmurs, or postural hypotension
- Weight (and comparison to previous weights if possible)

Diagnostic Investigations

The following may be helpful ancillary tests* but their completion should not delay referral:

- Fecal Occult Blood Test (FOBT), in the absence of current active rectal bleeding
- Complete blood count (CBC), and if low mean cell or corpuscular volume (MCV) (i.e., microcytic anemia), ferritin
- Imaging for abdominal masses

*Normal or negative results should not deter or delay referral. Positive results may increase the urgency of referral.

Referral

Wait times for a referral have been developed for the following indications by using evidence citing the relative predictability of the listed single or combined signs, symptoms, or diagnostic investigations for CRC and weighing this with the predictability for CRC of a positive FOBT in the Ontario CRC Screening Program (2). The referral wait times also align with the recommendations developed by the Canadian Association of Gastroenterology (3). In many jurisdictions, organized Diagnostic Assessment Programs (DAPs), with centralized referral access, facilitate timely tests and specialist appointments.

4. Referring physicians should send a referral to a CRC DAP or a specialist competent in endoscopy within 24 hours, expect a consultation within 2 weeks, and expect a definitive diagnostic workup to be completed within 2 weeks of consultation, if a patient has at least one of the following:
    - Palpable rectal mass suspicious for CRC
    - Abnormal abdominal imaging result suspicious for CRC

5. Based on a detailed history, physical examination, and investigations, along with clinical judgement, referring physicians should send a referral to a CRC DAP or a specialist competent in endoscopy within 24 hours, expect a consultation within 4 weeks, and expect a definitive diagnostic work up to be completed within 8 weeks of referral, if a patient has at least one of the following:
    - Unexplained rectal bleeding in patients with at least one of the following characteristics or combinations of symptoms:
        - Dark rectal bleeding
        - Rectal bleeding mixed with stool
        - Rectal bleeding in the absence of perianal symptoms
        - Rectal bleeding and change in bowel habits
        - Rectal bleeding and weight loss
    - Unexplained IDA and a hemoglobin of ≤110 g/L for males or ≤100 g/L for non-menstruating females

For patients where the decision to refer to a CRC DAP or a specialist has been made based on the above criteria, the following may increase the risk of CRC and may be taken into consideration to assist the specialist assessment in prioritizing patients.

- Patients aged 60 years and older with any of the above mentioned signs or symptoms
- Male patients with any of the above mentioned signs or symptoms
- A combination of any of the above mentioned signs or symptoms
- Patients with any of the above mentioned signs or symptoms and a first-degree family history of CRC

In situations where wait times may exceed these timelines, referring physicians may order (depending on locally available resources):

- Computed tomographic (CT) colonography
- Double-contrast barium enema (DCBE)

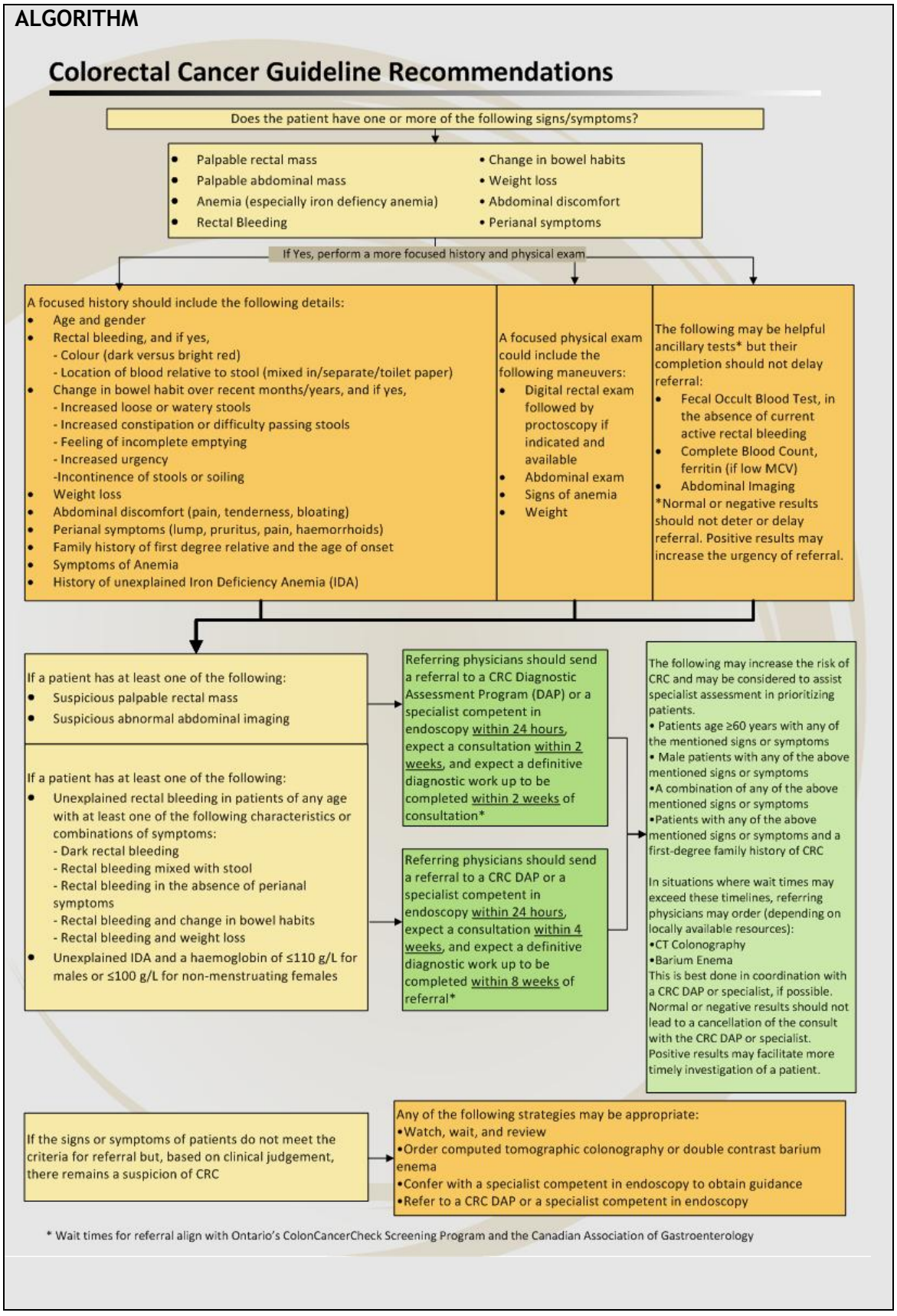
This is best done in coordination with the CRC DAP or specialist, if possible. Normal or negative results should not lead to a cancellation of the consult with the CRC DAP or specialist. Positive results may facilitate more timely investigation of a patient.

6. If the signs or symptoms of patients do not meet the criteria for referral but, based on clinical judgement, there remains a suspicion of CRC, then any of the following strategies may be appropriate:
   - Watch, wait, and review
   - Order CT colonography or DCBE
   - Confer with a specialist competent in endoscopy to obtain guidance
   - Refer to a CRC DAP or a specialist competent in endoscopy

Recommendations to Reduce Diagnostic Delay

- There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of CRC cancer for FPs and other PCPs.
- Educational tools should be developed on obtaining a proper detailed history, physical examination, appropriate investigations, and referral in patients presenting with suspicious signs and symptoms of CRC for FPs and other PCPs.
- During the periodic health examination, FPs and other PCPs should, at a minimum, ask patients who are 50 years of age or older about rectal bleeding, changes in bowel habits, and a family history for CRC.
- While discussing colorectal cancer screening with patients, FPs and other PCPs should ask about the signs and symptoms predictive of CRC.
- FPs and other PCPs should investigate unexplained anemia, especially IDA.
- For signs and symptoms suggestive of CRC with lower positive predictive values (PPVs) that may not have prompted initial referral, FPs and other PCPs should consider reassessment and further workup if the presentation does not resolve.
- FPs and other PCPs should consider implementing systems (e.g., open-access booking) to expedite initial appointments for patients calling with signs and/or symptoms suggestive of CRC.
- CRC DAPs and specialists competent in endoscopy should develop triage protocols to avoid delays in the diagnosis of CRC in patients with suspicious signs and/or symptoms.
- Sustainable public education about the signs and symptoms of CRC, the importance of early detection and management, as well as common fears and concerns that may delay referral, should be developed and implemented.
- Special efforts should be made to reduce delays in presentation often observed among women, single patients, younger patients, visible minorities, and patients with co-morbidities, decreased social support, lower levels of education, or a rural residence.

ALGORITHM


Colorectal Cancer Guideline Recommendations
Does the patient have one or more of the following signs/symptoms?
• Palpable rectal mass
• Palpable abdominal mass
• Anemia (especially iron defiency anemia)
• Rectal Bleeding
• Change in bowel habits
• Weight loss
• Abdominal discomfort
• Perianal symptoms
If Yes, perform a more focused history and physical exam
A focused history should include the following details:
• Age and gender
• Rectal bleeding, and if yes,
- Colour (dark versus bright red)
- Location of blood relative to stool (mixed in/separate/toilet paper)
• Change in bowel habit over recent months/years, and if yes,
- Increased loose or watery stools
- Increased constipation or difficulty passing stools
- Feeling of incomplete emptying
- Increased urgency
-Incontinence of stools or soiling
• Weight loss
• Abdominal discomfort (pain, tenderness, bloating)
• Perianal symptoms (lump, pruritus, pain, haemorrhoids)
• Family history of first degree relative and the age of onset
• Symptoms of Anemia
• History of unexplained Iron Deficiency Anemia (IDA)
A focused physical exam could include the following maneuvers:
• Digital rectal exam followed by proctoscopy if indicated and available
• Abdominal exam
• Signs of anemia
• Weight
The following may be helpful ancillary tests* but their completion should not delay referral:
• Fecal Occult Blood Test, in the absence of current active rectal bleeding
• Complete Blood Count, ferritin (if low MCV)
• Abdominal Imaging
*Normal or negative results should not deter or delay referral. Positive results may increase the urgency of referral.
If a patient has at least one of the following:
• Suspicious palpable rectal mass
• Suspicious abnormal abdominal imaging
Referring physicians should send a referral to a CRC Diagnostic Assessment Program (DAP) or a specialist competent in endoscopy within 24 hours, expect a consultation within 2 weeks, and expect a definitive diagnostic work up to be completed within 2 weeks of consultation*
If a patient has at least one of the following:
• Unexplained rectal bleeding in patients of any age with at least one of the following characteristics or combinations of symptoms:
- Dark rectal bleeding
- Rectal bleeding mixed with stool
- Rectal bleeding in the absence of perianal symptoms
- Rectal bleeding and change in bowel habits
- Rectal bleeding and weight loss
• Unexplained IDA and a haemoglobin of ≤110 g/L for males or ≤100 g/L for non-menstruating females
Referring physicians should send a referral to a CRC DAP or a specialist competent in endoscopy within 24 hours, expect a consultation within 4 weeks, and expect a definitive diagnostic work up to be completed within 8 weeks of referral*
The following may increase the risk of CRC and may be considered to assist specialist assessment in prioritizing patients.
• Patients age ≥60 years with any of the mentioned signs or symptoms
• Male patients with any of the above mentioned signs or symptoms
•A combination of any of the above mentioned signs or symptoms
•Patients with any of the above mentioned signs or symptoms and a first-degree family history of CRC
In situations where wait times may exceed these timelines, referring physicians may order (depending on locally available resources):
•CT Colonography
•Barium Enema
This is best done in coordination with a CRC DAP or specialist, if possible. Normal or negative results should not lead to a cancellation of the consult with the CRC DAP or specialist. Positive results may facilitate more timely investigation of a patient.
If the signs or symptoms of patients do not meet the criteria for referral but, based on clinical judgement, there remains a suspicion of CRC
Any of the following strategies may be appropriate:
•Watch, wait, and review
•Order computed tomographic colonography or double contrast barium enema
•Confer with a specialist competent in endoscopy to obtain guidance
•Refer to a CRC DAP or a specialist competent in endoscopy
* Wait times for referral align with Ontario's ColonCancerCheck Screening Program and the Canadian Association of Gastroenterology

KEY EVIDENCE

Clinical Presentation

The Working Group believe that the signs and symptoms listed under clinical presentation should inform FPs and other PCPs about the suspicion of CRC. The signs or symptoms listed met one of two criteria: the sign or symptom presented in at least 5% of patients with confirmed CRC, or the sign or symptom was a statistically significant predictor of CRC. The exception to this is perianal symptoms. The absence of perianal symptoms with rectal bleeding strengthens the PPV for CRC rather than the presence of perianal symptoms. The studies included in calculating median PPVs or that contained multiple regression analyses can be found in Section 2 of this report.

The signs and symptoms of anemia as well as the questions to ask patients presenting with unexplained anemia were derived from an evidence-based guideline for the management of anemia used by family physicians in the Working Group (4).

There was a paucity of studies examining the diagnostic accuracy of DRE and proctoscopy for predicting CRC in symptomatic patients. Therefore, these tests were included based on consensus, because a DRE is a simple manoeuvre, can be easily performed in primary care, and, if a suspicious rectal mass is felt, provide valuable information leading to expedited referral. Proctoscopy is also commonly used in the primary care setting.

Diagnostic Investigations

The following diagnostic investigations that were chosen by the Working Group may be helpful in completing an assessment: FOBT, complete blood count, and imaging for abdominal masses. These investigations may be ordered because a patient presents with certain signs or symptoms (i.e., signs of anemia and/or symptoms of an abdominal mass) that would lead to a referral, or these tests may be ordered to determine if other suspected signs or symptoms of CRC are present (i.e., FOBT). The results of these tests would be made available to the specialists.

The meta-analysis by Jellema et al (2010) found good diagnostic performance for both guaiac and immunological-based FOBT tests in symptomatic patients (5). Since a combination of symptoms or signs increases the likelihood of CRC (6), the Working Group believe patients with one sign or symptom and a concurrent positive FOBT (in the absence of current active rectal bleeding) should be triaged more urgently than should patients with only a single sign or symptom. Likewise, patients with single symptoms or signs who subsequently are found to have anemia or IDA should also be triaged more urgently than should patients with a single symptom.

Because there were very few studies examining the diagnostic accuracy of carcinoembryonic antigen (CEA) and erythrocyte sedimentation rate (ESR) for predicting CRC in symptomatic patients, they were not recommended. There were very few studies examining the diagnostic accuracy of a CBC alone, but there was consensus that this should be ordered to assist in the evaluation of whether anemia, and especially IDA, is present.

It is common practice to image abdominal masses found during a physical examination. Imaging may help to determine whether the mass is intra-colonic or extra-colonic and direct the workup of the mass, as well as indicate appropriate specialty referral.

Referral

The Working Group chose to include signs or symptoms with median PPVs greater than 10%, identified in studies in Section 2 of this report, as indicators for referral. The development of these recommendations can be found in Section 3 of this report.

The following combinations of clinical features have been found to increase the index of suspicion for CRC:

- Increasing age (most studies used a cutoff of greater than or equal to 60 years) and rectal bleeding or change in bowel habits or anemia (especially IDA)
- Male patients with rectal bleeding or change in bowel habits or anemia (especially IDA)
- A combination of signs or symptoms

Meta-analyses by Olde Bekkink et al and Jellema et al found high specificity but low sensitivity for a family history of CRC in symptomatic patients (5,7). Also, Jellema et al reported a pooled PPV of 6% for a family history of CRC in symptomatic patients (5). Based on the consensus of the Working Group, the decision was that patients with a first-degree family history of CRC might be at higher risk of CRC and should be priority triaged when referred according to the criteria described above. Regardless of symptoms, the current recommendation was that patients with a personal history of polyps or a first-degree family history of CRC should participate in a CRC screening surveillance program that includes regular colonoscopies.

If the time to referral exceeds the recommended wait times, the Working Group recommended that the referring physician order CT colonography or DCBE, depending on locally available resources. This would ensure that as much information as possible would be made available to the specialist during the consultation. There is some evidence to suggest that CT colonography or DCBE may have good diagnostic properties in symptomatic patients. The sensitivities and/or specificities were over 83% when CT colonography or DCBE were compared to colonoscopy alone (8-18). Flexible sigmoidoscopy (FS) also showed good sensitivity for detecting CRC, especially when combined with DCBE (9,12,16,19). However, the Working Group preferred that the entire colon be visualized. There were few studies examining the diagnostic accuracy of abdominal CT or abdominal or pelvic ultrasound among symptomatic patients.

Factors Contributing to Diagnostic Delay

Evidence from prospective and retrospective studies described in Section 2 of this report suggest that the following may delay the diagnosis of CRC:

- FP and other PCP-related delays (20-24)
  - failure to recognize signs and symptoms were suggestive of CRC
  - failure to investigate IDA
  - failure to perform DRE
  - initial referral to a specialist without a gastrointestinal interest
  - receiving inaccurate or inadequate tests
  - frequent visits following an inconclusive first visit
  - patients with colon cancer referred less quickly than patients with rectal cancer

- younger patients
- gender (females had longer delays than males)
- visible minorities

- Patient-related delays (20-23,25)
  - patient's lack of appreciation regarding the association of symptoms with CRC
  - fear that tests might be unpleasant or embarrassing
  - uncomfortable with or embarrassed about symptoms, including pain, nausea, and vomiting
  - decreased social support
  - presence of co-morbidity
  - rural residency
  - lower education level
  - single/separated/divorced
  - female colon cancer patients had longer delays than male
  - male rectal cancer patients had longer delays than females

FUTURE RESEARCH

Further studies should be designed to determine which educational initiatives would be best at decreasing practitioner or patient-related delay. Also, more studies to determine the diagnostic performance of signs and symptoms for CRC are needed in the primary care setting.

Methods

Targeted Peer Review: During the guideline development process, six targeted peer reviewers from Ontario and British Columbia considered to be clinical and/or methodological experts on the topic were identified by Colorectal Cancer Referral Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on June 20, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Colorectal Cancer Referral Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All health care professionals with an interest in colorectal cancer including family physicians, gastroenterologists, radiologists and surgeons in the PEBC database were contacted by email to inform them of the survey. Also, members of the Canadian Cancer Society, the Nurses Practitioner Association of Ontario, the Ontario College of Family Physicians, the Ontario Hospital Association, the Ontario Medical Association, and the Uniting Primary Care and Oncology Leads at Cancer Care Manitoba were invited to review this guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on June 20, 2011. The

consultation period ended on August 16, 2011. The Colorectal Cancer Referral Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Two responses were received from two reviewers. The key results of the feedback survey are summarized in Table 2.

Table 2. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	2	0
2. Rate the guideline presentation.	0	0	0	1	1
3. Rate the guideline recommendations.	0	0	1	1	0
4. Rate the completeness of reporting.	0	0	0	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	0	1
6. Rate the overall quality of the guideline report.	0	0	0	2	0
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	1	0	1
8. I would recommend this guideline for use in practice.	0	0	0	1	1

9. What are the barriers or enablers to the implementation of this guideline report?

The target peer reviewers felt the document was laid out well and the literature review was complete. One reviewer felt that education for primary care providers as well as resources for application and implementation should be considered. One reviewer mentioned that a primary care provider other than a family physician was not included in the working group. One reviewer mentioned they would have liked to have seen this guideline integrated with CRC screening guidelines.

Table 3. Summary of written comments by targeted peer reviewers and modifications/actions taken.

Summary of Written Comments	*Modifications/Actions/Comments*
1. The information on symptoms and signs of anemia are not generally practical and questionably useful.	The Working Group decided to shorten the list of signs and symptoms for anemia and refer physicians to (10,11).
2. I would have liked a comparison of the value of an in office digital sample for FOBT vs lab-ordered FOBT.	There is lack of evidence for this among symptomatic patients.

Professional Consultation: Ninety-eight of 418 (23%) responses were received. Key results of the feedback survey are summarized in Table 4.

Table 4. Responses to four items on the professional consultation survey.

	Number				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	*1*	*2*	*9*	*54*	*32*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	*4*	*7*	*13*	*33*	*40*
3. I would recommend this guideline for use in practice.	*1*	*2*	*14*	*39*	*42*

4. What are the barriers or enablers to the implementation of this guideline report?

Some professional consultants believed that the document was well organized and the evidence was extensively reviewed, whereas other reviewers believed the guideline was lengthy. As well, some reviewers believed the flowchart was useful, and others believed it was too complex. One reviewer suggested that an enabler would include province-wide organized diagnostic assessment programs with specific personnel available to answer questions about signs/symptoms/referral. Barriers included lack of resources, availability of specialists, and access to endoscopy and diagnostic investigations. Some reviewers believed that dissemination and education to a wide range of primary care givers is a challenge. Also, patients find it difficult to discuss any matters relating to excretory function. One reviewer felt an integrated provincial eReferral & reporting system is required to optimize system performance and patient outcomes. Although these guidelines will help move clinical practice in the right direction, without systematic infrastructural support, adoption will be limited.

Table 5. Summary of written comments by professional consultants and modifications/actions taken.

Summary of Written Comments	***Modifications/Actions/Comments***
1. A stronger comment or disclaimer that this guideline is NOT about asymptomatic screening, or screening with ONLY a positive family history.	Under target population "In addition, this guideline does not address CRC screening for asymptomatic patients." was added.
2. Screening symptom of 'change in bowel habit and 'abdominal discomfort' seem v. vague. Focused history and physical seems a lot to fit into a typical 15' visit- could there be any way of passing this down to key symptoms and/or signs?	The Working Group believe the recommendations give direction as to focusing on key symptoms and signs and is achievable in 15 minutes.
3. In regards to Q2 I am a ClR surgeon. I think DRE should be included without the "if available and indicated". You mention that omission of DRE is a reason for delay in dx. FPs/PCP don't like doing DRE so that line gives then an excuse not to.	The Working Group agreed and removed "if available and indicated".

4. Comments about the lack of usefulness of CEA for screening and initial investigation should be put in the main part of the guideline.	The Working Group believe the lack of usefulness of CEA is mentioned in the key evidence section and described more fully in section two. The Working Group chose not to make any changes.
5. Perhaps be more specific that abdominal imaging should be based on physical findings, not an option as part of routine work-up.	The Working Group agreed and made the changes suggested.
6. Lack of clarity on use of FOBT as diagnostic test for symptomatic patients.	The Working Group agreed and made changes to the recommendations regarding FOBT. They recommend it may be used in situations where FPs have a low level of suspicion of CRC.
7. I'm concerned re FOBT being used inappropriately. i.e. if negative - no further work-up.	The Working Group included the statement that "A negative result does not rule out CRC".
8. Many felt the timelines for referral were unrealistic.	These sentences were added under Target Population, "The guidelines are also intended for policymakers to help ensure that resources are in place so that target wait times can be achieved. They are intended to coincide with the introduction of colorectal cancer Diagnostic Assessment Programs (DAPS) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast-tracking of diagnostic tests and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to improve patient access and outcomes, and are outlined in the Ontario Cancer Plan since 2005-2011 and 2011-2014 (12)."
9. Indicate that the hemoglobin trend, especially with IDA, may be more important than absolute values.	The Working Group believed that this should be part of clinical judgement that influences a low or high index of suspicion.
10. Pg. 4 at top rectangle, 2nd bullet --> why limit to males with signs and symptoms when female sex is a barrier to early detection. These 2 statements are not congruous. Acknowledging that the deficiency is common in women, especially pre-menopausal women, why not add a category of older women with similar signs and symptoms.	The Working group chose not to change the recommendation because it aligns with the evidence. Also, stating that males have higher PPVs in the recommendations is for triaging purposes and not an indication for referral.
11. Expecting consultation before colonoscopy is often unwarranted; in many instances the need for colonoscopy is clear and could be directly booked without consultation. This is often done	This is outside the scope of this document. This document sets what timelines should ideally exist. How a community of practitioners or DAP get

where there is a close relationship between consultant and FP when need is urgent - why cannot it be expected in all instances. A corollary is that when patients have to travel far distances for their consultation (e.g. northern Ontario) investigations should be coordinated so that repeat trips are not required.	there is for discussions locally, regionally, provincially with service providers/ administrators. FP's refer to an endoscopist who then decides if the scope is warranted. It may be to a particular endoscopist or to a clinic or DAP who 'assigns' the endoscopist.
12. Eliminate DCBE due to poor sensitivity & declining quality/expertise	The Working Group chose not to change this recommendation because there is evidence in the literature indicating its usefulness and there may be value in ordering DCBE when there are delays to colonoscopy.
13. In #3 (page 4) & algorithm, "if suspicion for CRC", I do not suggest "watch, wait, and review" statement unless a reasonable timeframe is suggested (not 'open ended').	The Working Group agreed and made this recommendation more specific.
14. What is the evidence of educational validity of any educational tool - Please reference What is sustainable education (I have pursued a MEd and am unfamiliar with this concept) Please provide a definition of this term. What specific educational methodologies are shown to have significant benefit in achieving this goal? As this is an evidence based guideline, you are obligated to present evidence of the efficacy of such methodologies. Otherwise you should admit that this is a motherhood statement but without adequate literature to actually support the " educational " recommendations.	The recommendations were changed to "Information regarding the signs and symptoms of CRC, how to obtain a proper detailed history, physical examination, appropriate investigations, and referral of patients presenting with suspicious signs and symptoms should be widely disseminated to FPs and other PCPs using various knowledge translation strategies."
15. Pg. 4, under recommendations, 6th bullet, what are the signs and symptoms associated with lower PPV. Not listed ? not have section 2 & 3.	The recommendation was reworded to "For signs and symptoms suggestive of CRC that may not have prompted initial referral, FPs and other PCPs should reassess and further workup if sign/symptoms do not resolve."
16. Under "Recommendation to reduce diagnostic delays" - don't feel that the statement regarding appointment booking system should be included in such a guideline as this should be at the discretion of the physician, a recommendation about office staff triaging suspicious complaints for CRC would be more accurate.	The recommendation was reworded to "FPs and other PCPs should consider training staff regarding triaging of patients calling with signs and/or symptoms suggestive of CRC to expedite initial appointments."
17. Some comment regarding what to do in event of positive screening FOBT on the algorithm would be helpful.	The Working Group changed the title to "Colorectal Cancer Guideline Recommendations for Symptomatic Patients" to reflect that this guideline is not for screening.

18. Suggestion - a simple CRC form for referrals with check boxes for history & physical exam - history part can be filled in by patients and PE part checked in by primary physicians - would get more information from primary physicians and also remind physicians to perform the DRE - most of my colleagues do not perform either a DRE or anoscopy in clinics - form will also increase patient acceptance of the procedure.	The Working Group agreed with this comment and believed this guideline could be used to development these knowledge translation products.
19. Quality information from referring practitioners remains a major obstacle in prioritizing referrals on this topic. I wonder if a referral sheet incorporating the features of the guideline recommendations flowchart in a concise fashion would be helpful. Perhaps a tick-off format would make it easy to enter info. Documentation of investigations completed to date with results would be valuable. Inadequate or incomplete info frequently delays assessment.	See #19.

Review by the CRC Advisory Committee

The CRC Advisory Committee provided feedback to the Working Group during a teleconference on January 17, 2012. Two gastroenterologists from the committee, Drs. Michael Gould and Jill Tinmouth, provided written feedback to the Working Group. The responses to their feedback can be found in Table 6. The Expert Panel approved the changes made by the Working Group.

Table 6. Summary of written comments by CRC Advisory Committee and modifications/actions taken.

Summary of Written Comments	*Modifications/Actions/Comments*
1. The evidence to support FOBTs is largely based on the Jellema et al 2010 review, which includes studies mainly from secondary care (9). I believe that the patients in these studies differ importantly from typical primary care symptomatic patients as most had already been triaged to colonoscopy. This suspicion is substantiated by the very high prevalence of CRC in these studies: 1-15%, with 11 studies reporting prevalence ≥ 5%. This is much higher than the prevalence of CRC in most primary care settings, even among symptomatic patients. Given that PPV varies with the prevalence of the disease in the population, I would be very hesitant to apply the PPV reported in the Jellema et al 2010 study to settings that are truly primary care.	The Working Group agreed that the majority of studies in the Jellema et al 2010 systematic review were conducted in secondary care settings and that this was a concern (9). However, Jellema et al 2010 selected secondary care studies with a prevalence of CRC of less than 15% because this was the highest prevalence seen in their included primary care studies. It is difficult to know whether this is significantly different than the prevalence of CRC among symptomatic patients in the primary care setting without evidence to support that claim.
2. Where reported, the mean/median age from the studies in the Jellema et al 2010 paper	Young patients have been found to have delays in diagnosis. This delay would

suggests that older populations were studied; the reported PPV would be affected by the higher prevalence of CRC in these populations (9). The PEBC review does not comment on or advise regarding the age of symptomatic patients in whom an FOBT might be considered. I would be concerned that as a result, readers might also use the FOBT in younger symptomatic patients.	not be offset by participation in CRC screening as they are not invited to participate. The work-up of symptoms in this small group may reduce delay in diagnosis. The Working Group believed that a younger patient with symptoms of CRC that did not meet the criteria for referral (ex., change in bowel habits) could be offered a FOBT in addition to treating their symptoms if their suspicion for CRC was low. Many of the studies that examined symptomatic patients included younger patients. So, although the prevalence of CRC is lower in younger patients, patients with symptoms have a higher risk for CRC than asymptomatic patients. If a FP has a lower suspicion of CRC for a younger symptomatic patient (ex., with a change in bowel habits), a FOBT could be ordered to assist the FP in deciding whether to refer (with a positive FOBT) or treat and review (with a negative FOBT).
3. Application of the algorithm states that patients with a rectal mass, rectal bleeding, iron deficiency anemia or abnormal imaging warrant urgent referral. The implication is that FOBT may be useful in the remaining symptomatic patients to "increase the urgency of the referral". However, 16 of the 19 studies in the Jellema et al 2010 paper took all symptomatic patients (3 excluded patients with visible rectal bleeding) (9). I suspect that many of the patients in these studies had the more worrisome symptoms (as described by the PEBC doc) warranting urgent referral mentioned above – and these patients are likely driving the high PPV reported in the Jellema et al 2010 paper. As a result, I would be cautious about using FOBT in the subset of symptomatic patients (ie symptoms other than rectal mass, rectal bleeding, or iron deficiency anemia) described in the PEBC algorithm in the PEBC review as I do not think the PPV would be as high as reported by Jellema et al 2010.	The Working Group agreed this was a limitation of the studies in the Jellema et al article, however, patients with the remaining unexplained symptoms (ex., change in bowel habits or weight loss) are still at higher risk for CRC than asymptomatic patients (9). According to the evidence, combinations of signs and/or symptoms increase the PPV for CRC (see Section 2 of this report). Having a positive FOBT in addition to another symptom should increase the PPV for CRC. Therefore, the Working Group believed that in cases where FPs had a lower suspicion of CRC for the remaining symptomatic patients, a FOBT could be used to assist the FP in deciding whether to refer or treat and review.
4. Despite the statement in the PEBC review that a negative FOBT result should not deter or delay referral, I think that it would. Otherwise, why bother doing the test?	The Working Group agreed with this comment and changed the recommendations to include a treat-

	and-review statement if the FOBT was found to be negative.
5. Should the family doctor be concerned about symptoms, they should treat the symptoms and then refer if there is concern or no improvement, or just refer the patient. The regular referral pathway when there is heightened concern should be used if the referral needs to be expedited. While I do share the concern about screening patients jumping the queue over symptomatic patients, it requires good family doctor-consultant communication to deal with the issue.	The Working Group agreed with this concern and divided the remaining symptomatic patients into those where the FP had a lower suspicion of CRC and those where the FP had a higher suspicion of CRC. The Working Group recommended referring patients where there was a high level of suspicion and treating and reviewing patients (which could include a FOBT) where there was a low level of suspicion. The Working Group also chose to remove FOBT as a test to increase the urgency of referral because semi-urgently and urgently referred patients are recommended to be seen at least as quickly as asymptomatic patients with a positive FOBT.
6. The CCO colon check program is a population based screening program and not meant to deal with GI symptoms and we should not be using the screening kits for that purpose, and we should be promoting this approach through the CCO colon check program.	The Working Group agreed with this concern and included FOBT (non-ColonCancerCheck) in their recommendations to reflect that the FOBT kits ordered should not be screening kits. The Working Group also included a statement that three stool samples should be taken at three different bowel movements.
7. I reviewed the members of the expert panel, absent among the members were any Gastroenterologists who are arguably the experts in this field. I believe this was a significant oversight, which lead you to this place.	The Working Group acknowledged this concern and had difficulty in recruiting gastroenterologists to volunteer as expert panel members. The Working Group is appreciative to Drs. Gould and Tinmouth for providing their valuable feedback to make this guideline a better document.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Colorectal Cancer Referral Expert Panel and the Director of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Evidence-Based Series 24-1: Section 4 – Document Review

Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers

L. Del Giudice, X. Yao, S. Kellett, and The Colorectal Cancer Referral Expert Panel

April 10, 2017

The 2012 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012. In January 2015, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (LDG) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Colorectal Cancer Referral Expert Panel members (Appendix 1) endorsed the recommendations found in Section 1 (Guideline Recommendations) on April 10, 2017.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. How should patients presenting to family physicians (FPs) and other primary care providers (PCPs) with signs and/or symptoms of colorectal cancer (CRC) be managed? What signs, symptoms, and other clinical features that present in primary care are predictive of CRC?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of CRC?
3. What major, known risk factors increase the likelihood of CRC in patients presenting with signs and/or symptoms of CRC?

4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

Literature Search and New Evidence

PEBC has decided to focus on existing systematic reviews and clinical practice guidelines for this updated literature search. The new search (June 2009 to September 2015) yielded a total of two existing guidelines and three systematic reviews. The results of the included guidelines and systematic reviews can be found in the Document Review Tool below.

Impact on Guidelines and Its Recommendations

The new evidence continues to support current recommendations. However, the new evidence slightly weakens some of the recommendations. For example, median positive predictive values for such specific symptoms as anemia and rectal bleeding may be slightly lower according to new evidence. Compared with the new 2015 NICE guidelines, the recommendations in this guideline are more conservative and have a lower threshold for the gold standard investigation using colonoscopy, based on the same evidence.

During the review process, an issue was raised with respect to the option to test with FOBT in a narrow set of circumstances. In the 2017 version, because of the possible negative impact of the 2012 recommendation regarding FOBT on the organized colorectal cancer screening program in Ontario, it was decided to remove all recommendations associated with FOBT from the guidance for referral, from the summary of key evidence, and from the accompanying algorithm

With those minor changes, the Colorectal Cancer Referral Expert Panel ENDORSED the 2012 recommendations.

Document Review Tool

Number and title of document under review	EBS 24-1: Referral of Patients with Suspected Colorectal Cancer by Family Physicians and Other Primary Care Providers
Current Report Date	April 24, 2012
Clinical Expert	Lisa Del Giudice
Health Research Methodologists	Xiaomei Yao and Sarah Kellett
Date Assessed	January 6, 2015
Current Literature Search Date	September 8, 2015
Approval Date	April 10, 2017
Original Questions: 1. How should patients presenting to family physicians (FPs) and other primary care providers (PCPs) with signs and/or symptoms of colorectal cancer (CRC) be managed? What signs, symptoms, and other clinical features that present in primary care are predictive of CRC? 2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of CRC? 3. What major, known risk factors increase the likelihood of CRC in patients presenting with signs and/or symptoms of CRC?	

4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

Target Population:
Adult patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients who present with alarming emergency symptoms and signs of hemodynamic instability, acute gastrointestinal hemorrhaging, acute intestinal obstructions, or unremitting abdominal pain. These patients should be immediately referred to emergency for assessment and treatment. In addition, this guideline does not address CRC screening for asymptomatic patients.

Study Section Criteria:
Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG or NICE guidelines, and included recommendations not found or different from those in either the NICE or NZGG guidelines.

Studies, found from reference lists, that were published before the NICE or NZGG guidelines but were not included in their reports were included in this systematic review if they addressed any of the research questions and met the inclusion criteria.

This report focuses on adult patients presenting to primary care with signs or symptoms of CRC. For the clinical question regarding the predictive characteristics of signs or symptoms, all comparative studies of symptom recognition and/or identification for CRC were included. Studies that reported only the main signs or symptoms for each patient, ignoring the presence of additional signs or symptoms, were excluded. Studies where CRC was found in only one patient were also excluded. Studies conducted in secondary care settings were included if they provided predictive information about signs and/or symptoms for suspected CRC; however, they may not have been taken as strongly into consideration as were primary care data when developing the recommendations. Screening studies were excluded because they include asymptomatic patients.

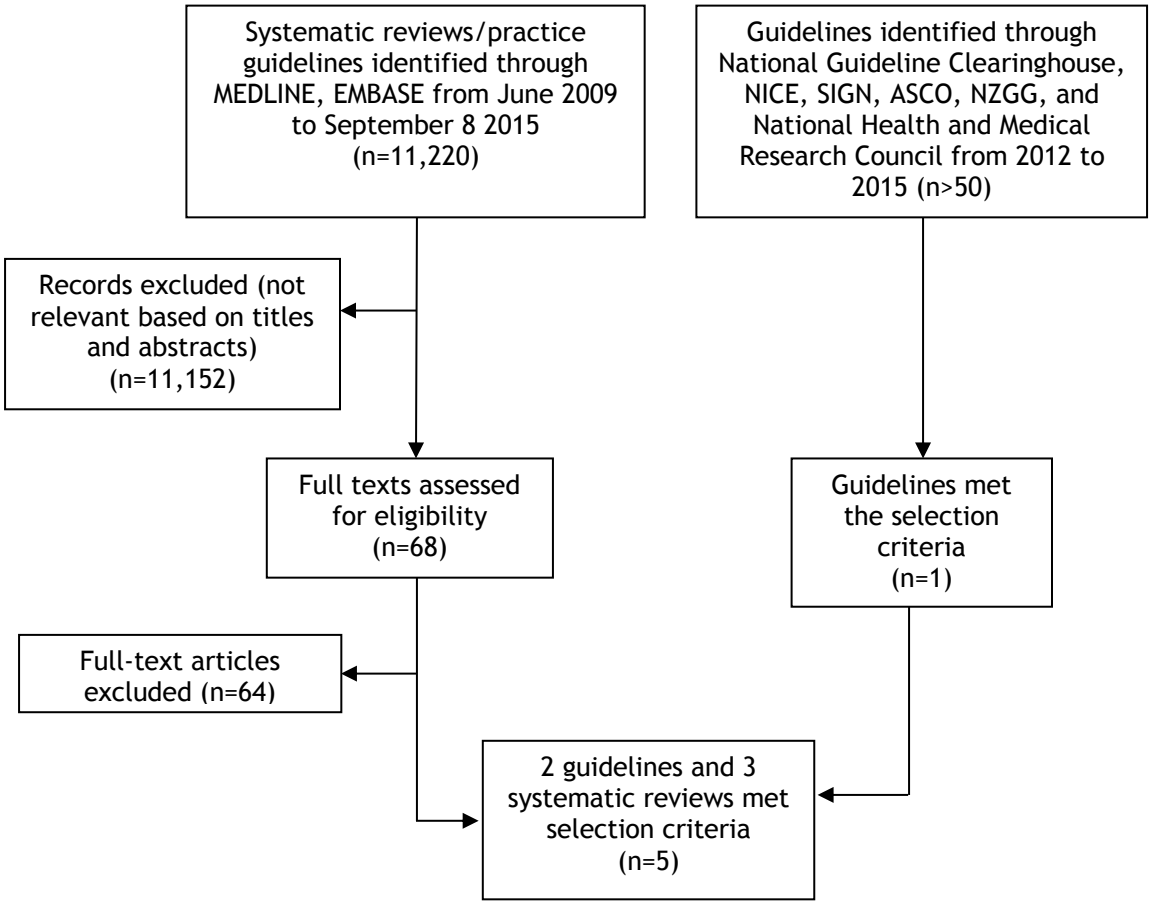
All diagnostic studies were sought in which adult symptomatic primary care patients underwent one or more investigations that included computed tomographic (CT) colonography, barium enema, sigmoidoscopy, ultrasound, CT scan, digital rectal examination (DRE), proctoscopy, rectoscopy, anoscopy, fecal occult blood tests (FOBTs), or complete blood counts (CBC). Studies involving investigations for carcinoembryonic antigen (CEA), C-reactive protein, erythrocyte sedimentation rate (ESR), ferritin, or serum iron were also searched. Studies conducted in secondary care settings were included if they provided diagnostic information for suspected CRC for the specified investigations; however, they may not have been considered as strongly as the primary care data when developing the recommendations. Screening studies were excluded.

For the clinical questions concerning risk factors and delay, a search for practice guidelines, systematic reviews with meta-analyses, and systematic reviews without meta-analyses was performed. If these articles did not definitively answer the particular clinical question, searches for randomized phase III trials and randomized phase II trials, followed by comparative studies, were performed. If the information from systematic reviews definitely answered the question(s), articles from the time of publication of the systematic review and onwards were searched. To develop recommendations with feasible wait times for Ontario, articles assessing wait times in Canada were also included, regardless of study design.

Non-English publications were not eligible due to the lack of translation funding. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Search Details:
Please see the search strategy for Medline and Embase in Appendix 2.

Brief Summary/Discussion of New Evidence:
PEBC decided to focus on existing systematic reviews and clinical practice guidelines for this updated literature search. The flow diagram of existing systematic reviews and clinical practice guidelines considered in this review is shown below:



NICE = National Institute for Health and Care Excellence, SIGN = Scottish Intercollegiate guidelines Network, ASCO = American Society of Clinical Oncology, NZGG = New Zealand Guidelines Group

Two guidelines and three SRs met the inclusion criteria and are summarized in Table 1. There is no SR or guideline eligible for Q3. Nine of 12 eligible studies in the Huggenberger 2015 SR were covered by the Tong 2014 SR for Q1.

Table 1. Systematic Reviews/guidelines

Q1: Symptoms/signs

References	Study	Sample size	Pts population	Outcome	Brief results
NICE 2015 (guideline) [1]	31	Unclear	Pts with symptoms for suspicious CRC in primary care settings	PPV	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if: • they are aged 40 and over with unexplained weight loss and abdominal pain or

					• they are aged 50 and over with unexplained rectal bleeding or • they are aged 60 and over with: iron-deficiency anemia or changes in their bowel habit, or • tests show occult blood in their feces (see final recommendation in this list for who should be offered a test for occult blood in feces). **[new 2015]** Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people with a rectal or abdominal mass. **[new 2015]** Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain • change in bowel habit • weight loss • iron-deficiency anemia. **[new 2015]**
Huggenberger 2015 [2]	12	NR	Unselected population from general practice with a newly recognised alarm symptom	PPV or LR for any of the alarm symptoms	PPV of "rectal bleeding" was high for patients > 60 years (6.6-21.2%), but much lower in younger age groups. For "change in bowel habits" and "significant general symptoms", the PPV was 3.5-8.5%.
Tong 2014 [3]	38	73,174 Pts with RB (5,626 CRC Pts)	24 primary care settings, 9 secondary hospital settings, 5 community settings	SEN, SPE, PPV	Diagnostic values for RB: SEN=47% (CI=45%-48%), SPE=96% (CI=96%-96%), PPV=6% (CI=5%-8%).
Q2: Investigation tests					
References	**Study**	**Sample size**	**Pts population**	**Tests**	**Brief results**
NICE 2015 (guideline) [1]	12	Unclear	Pts with symptoms for suspicious CRC in primary care settings	FOBT, Sigm, Double-contrast barium enema	Offer testing for occult blood in feces to assess for colorectal cancer in adults without rectal bleeding who: • are aged 50 and over with unexplained: abdominal pain or weight loss, or • are aged under 60 with changes in their bowel habit or iron-deficiency anemia or • are aged 60 and over and have anemia even in the absence of iron deficiency. **[new 2015]** The fecal occult blood testing is cost-effective to detect colorectal cancer in people aged 40 years and older with a change in bowel habit in primary care. Barium enema, flexible sigmoidoscopy and computed tomography colonography were all found to be cost-effect compared to colonoscopy however FOBT was the most cost effective for this low risk population. Discuss with people with suspected cancer (and their carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations including their potential risks and benefits. **[new 2015]**
Spada 2015 (ESGE/ESGAR guideline) [4]	NR	NR	Pts with symptoms or without symptoms	CTC	a) ESGE/ESGAR recommend CTC as the radiological examination of choice for the diagnosis of colorectal neoplasia. b) ESGE/ESGAR do not recommend barium enema in this setting (strong recommendation, high quality evidence).

Q3: Risk factors in symptomatic pts for CRC: no evidence was found

Q4: Delay

References	Study	Sample size	Inclusion criteria	Brief results
Oberoi 2014[a] [5]	32	6-1,966 per study	a) Focused on factors associated with delay between the onset of symptom and seeking medical advice b) Had adequate sample size and provided statistically significant differences with regards to factors associated with delay (quantitative) and those with rigorous methods of data collection and analysis (qualitative)	**Factors that increased patient delay:** ***Demographic factors*** . Educational level (low) . Younger age (< 50 years) in men and older age in women . Lack of health insurance . Low income . Living with spouse (rectal cancer) . Living in rural areas . Inadequate transportation facilities . Difficulty in visiting GP or making appointment . No screening advice received from the doctor . Lack of social support or lay referral networks ***Health belief factors*** . Non-specific symptoms . Attribution of symptoms to benign conditions and non-recognition of symptom severity . Attribution of symptoms to changes in diet and lifestyle . Fear of unpleasant investigations . Fear of treatment . Denial of cancer . Lack of trust in the medical system . Belief that the symptoms would resolve spontaneously . Past history of anxiety and depression or of benign bowel disease . Family history of cancer . Relief from over-the-counter medications **Factors that reduced patient delay:** ***Demographic factors*** . Age (> 60 years) for males . Retirement . Educational level (high) ***Health belief factors*** . Persistent symptoms . Aggravation of symptoms . Blood mixed in stool . Abdominal pain and discomfort . Multiple symptoms occurring together . Trust in GP . Symptom disclosure to someone significant . Knowledge about the cause of symptoms . Opportunity to talk to GP about lower bowel symptoms during regular visit **Factors that had a mixed impact on delay:** . Embarrassment about the symptoms . Fear of cancer diagnosis . Not living with spouse . Socioeconomic status

Abbreviations: AUC=Area under curve, BMI = body mass index, CI = 95% confidence interval, CRC = colorectal cancer, CTC = computed tomographic colonography, ESGE/ESGAR = European society of gastrointestinal endoscopy and European society of gastrointestinal and abdominal radiology, LR = likelihood-ratios, NR = not reported, PPV = positive predictive values, Pts = pateints, RB = rectal bleeding, RR = risk ratio, SEN = sensitivity, Sigm = sigmoidoscopy, SPE = specificity

[a] The blue highlighted factors were not mentioned in 24-1 guideline for patients-related delay factors.

Clinical Expert Interest Declaration:
No conflict of interest was declared.

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	NO
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	YES YES
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	NO
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	UNCERTAIN

Review Outcome	ENDORSED
DSG/GDG Approval Date	April 10, 2017
DSG/GDG Commentary	In the future, a review of FIT as a diagnostic test in the evaluation of patients with symptoms suspicious of colorectal cancer should be considered.

New References Identified:

[1] National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2015 [cited 2015 November 12]. Available from http://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-1837268071621.
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[5] Oberoi DV, Jiwa M, McManus A, Hodder R. Colorectal cancer--applying a gender lens. Qual Prim Care 2014;22:71-9.

Appendix 1. Members of the Expert Panel

Name	Affiliation
Lisa Del Giudice, MD, MSc, CCFP	CCO Regional Primary Care Lead Toronto Central Regional Cancer Program Toronto, Ontario
Danusia Gzik, MD, MHSc, CCFP	CCO Regional Primary Care Lead North Simcoe Muskoka Regional Cancer Program Huntsville, Ontario
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Appendix 2. Search Strategies

For Question 1 (Symptoms/signs)
Systematic Reviews Only
Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp "sensitivity and specificity"/
2 false negative reactions/ or false positive reactions/

3 (sensitivity or specificity or accura$).ab,ti.
4 diagnos$.ab,ti.
5 predictive value$.ab,ti.
6 reference value$.ab,ti.
7 ROC.ab,ti.
8 (likelihood adj ratio$1).ab,ti.
9 monitoring.tw.
10 (false adj (negative$1 or positive$1)).ab,ti.
11 (systematic adj (review: or overview:)).mp.
12 (meta-analy: or metaanaly:).mp.
13 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
14 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
15 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
16 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
17 or/1-16
18 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
19 (stud: adj1 select:).ab.
20 (18 or 19) and review.pt.
21 17 or 20
22 (guideline or practice guideline).pt.
23 exp consensus development conference/
24 consensus/
25 (guideline: or recommend: or consensus or standards).ti.
26 22 or 23 or 24 or 25
27 21 or 26
28 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case reports or historical article).pt.
29 27 not 28
30 exp body weight changes/
31 (weight adj1 loss$).tw.
32 exp "signs and symptoms, digestive"/
33 cachexia.tw.
34 (loss adj2 appetite).tw.
35 early satiety.tw.
36 Anorexia/
37 anorexia.tw.
38 "nausea and vomiting"/ or nausea/ or vomiting/
39 nausea.tw.
40 vomiting.tw.
41 gastrointestinal hemorrhage/ or melena/
42 ((abdom$ or stomach or back or flank) adj3 pain).tw.
43 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw.

44 ((abdom$ or stomach or rect$ or colorectal or renal or intestin$ or gastrointestin$) adj3 mass$).tw.
45 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw.
46 obstruction$.tw.
47 ((gastrointestina$ or intestin$) adj (bleed$ or hemorrhag$ or haemorrhag$)).tw.
48 gastrointestinal hemorrhage/ or melena/
49 ((rect$ or colorect$) adj3 (bleed$ or hemorrhag$ or haemorrhag$)).tw.
50 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw.
51 ((mucus or pass$ mucus) adj stool$).tw.
52 stips$.tw.
53 (melena or maelena).tw.
54 Hematuria/
55 (hematuria or haematuria).tw.
56 (hematochezia or haematochezia).tw.
57 exp anemia/
58 (anemia or anaemia).tw.
59 (iron adj deficiency adj (anemia or anaemia)).tw.
60 exp Jaundice/
61 jaundice.tw.
62 exp Diarrhea/
63 (diarrhea or diarrhoea).tw.
64 change$ in bowel habit$.tw.
65 bowel habit change$.tw.
66 frequency of defecation.tw.
67 ((foecal or fecal) and incontinen$).tw.
68 continen$.tw.
69 constipat$.tw.
70 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw.
71 exp Cholecystitis/
72 cholecystitis.tw.
73 Ascites/
74 ascites.tw.
75 Hepatomegaly/
76 (hepatomegaly or hepato megaly).tw.
77 (alarm adj1 (symptom$ or sign$)).tw.
78 or/30-77
79 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or exp liver neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/
80 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw.
81 or/79-80
82 29 and 81 and 78
83 limit 82 to (english language and humans)

84 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ed.
85 83 and 84

Database: EMBASE
Search Strategy:
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1 "sensitivity and specificity"/
2 false negative result/ or false positive result/
3 (sensitivity or specificity or accura$).ab,ti.
4 diagnos$.ab,ti.
5 predictive value$.ab,ti.
6 reference value$.ab,ti.
7 ROC.ab,ti.
8 (likelihood adj ratio$1).ab,ti.
9 monitoring.tw.
10 (false adj (negative$1 or positive$1)).ab,ti.
11 (systematic adj (review: or overview:)).mp.
12 (meta-analy: or metaanaly:).mp.
13 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
14 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
15 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
16 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
17 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
18 (stud: adj1 select:).ab.
19 (17 or 18) and review.pt.
20 or/1-16
21 19 or 20
22 consensus development conference/
23 practice guideline/
24 *consensus development/ or *consensus/
25 *standard/
26 (guideline: or recommend: or consensus or standards).kw.
27 (guideline: or recommend: or consensus or standards).ti.
28 or/22-27
29 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30 (21 or 28) not 29
31 weight reduction/
32 (weight adj1 loss$).tw.
33 Cachexia/
34 cachexia.tw.
35 (loss adj2 appetite).tw.
36 early satiety.tw.
37 Anorexia/
38 anorexia.tw.
39 "nausea and vomiting"/ or nausea/ or vomiting/
40 nausea.tw.
41 vomiting.tw.
42 abdominal pain/ or lower abdominal pain/

43 digestive system hemorrhage/ or exp gastrointestinal hemorrhage/ or exp duodenum bleeding/
44 ((abdom$ or stomach or back or flank) adj3 pain).tw.
45 (pruritus ani or (itch$ adj3 anus) or (pain adj 3 defec$)).tw.
46 ((abdom$ or stomach or rect$ or colorectal or renal or intestin$ or gastrointestin$) adj3 mass$).tw.
47 (intestinal obstruction or acute intestinal obstruction or (obstruct$ adj intestin$) or (perforat$ adj intestin$)).tw.
48 obstruction$.tw.
49 ((gastrointestina$ or intestin$) adj (bleed$ or hemorrhag$ or haemorrhag$)).tw.
50 ((rect$ or colorect$) adj3 (bleed$ or hemorrhag$ or haemorrhag$)).tw.
51 ((rect$ or anal) and (bleed$ or blood$ or haemo$ or hemo$)).tw.
52 ((mucus or pass$ mucus) adj stool$).tw.
53 stips$.tw.
54 (melena or maelena).tw.
55 Hematuria/
56 (hematuria or haematuria).tw.
57 (hematochezia or haematochezia).tw.
58 exp anemia/
59 (anemia or anaemia).tw.
60 (iron adj deficiency adj (anemia or anaemia)).tw.
61 exp Jaundice/
62 jaundice.tw.
63 exp Diarrhea/
64 (diarrhea or diarrhoea).tw.
65 change$ in bowel habit$.tw.
66 bowel habit change$.tw.
67 frequency of defecation.tw.
68 ((foecal or fecal) and incontinen$).tw.
69 continen$.tw.
70 constipat$.tw.
71 (soil$ or diarrhoea$ or steatorrhoea$ or loose stool$ or loose motion$ or loose bowel motion$).tw.
72 exp Cholecystitis/
73 cholecystitis.tw.
74 exp Ascites/
75 ascites.tw.
76 Hepatomegaly/
77 (hepatomegaly or hepato megaly).tw.
78 (alarm adj1 (symptom$ or sign$)).tw.
79 or/31-78
80 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp liver cancer/ or exp intestine cancer/ or exp liver tumor/ or exp intestine tumor/
81 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw.
82 or/80-81
83 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ew.
84 79 and 82 and 30
85 83 and 84
86 limit 85 to (human and english language)

For Question 2 (Investigation tests)

Database: Ovid MEDLINE(R)
Search Strategy:
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1 Primary Health Care/
2 Physicians, Family/
3 ((family or general) adj practitioner$).mp.
4 gp.mp.
5 family physician$.mp.
6 family doctor$.mp.
7 Family Practice/
8 ((family or general) adj practice$).mp.
9 primary care.mp.
10 primary health care.mp.
11 or/1-10
12 meta-analysis/
13 "review literature".mp.
14 meta-analy$.mp.
15 metaanal$.mp.
16 (systematic$ adj (review$ or overview$)).mp.
17 meta-analysis.pt.
18 review.pt.
19 review.ti.
20 or/12-19
21 Case Reports/
22 letter.pt.
23 historical article.pt.
24 comment.pt.
25 (editorial or abstracts).pt.
26 or/21-25
27 20 not 26
28 exp "sensitivity and specificity"/
29 (sensitivity or specificity).tw.
30 exp Diagnostic Errors/
31 predictive value$.tw.
32 "Predictive value of tests"/
33 ROC.tw.
34 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw.
35 (false adj (negative or positive)).tw.
36 accuracy.tw.
37 reference value$.tw.
38 likelihood ratio$.tw.
39 ((pre-test or pretest) adj probability).tw.
40 post-test probability.tw.
41 Diagnosis, differential/
42 Diagnostic tests, routine/
43 or/28-42
44 exp Blood Cell Count/
45 (CBC or FBC or full blood count).tw.
46 C-reactive protein/
47 c-reactive protein$.mp.
48 Blood sedimentation/
49 erythrocyte sedimentation rate.mp.
50 ferritin.mp. or Ferritins/
51 serum iron.mp.
52 Occult blood/

53 stool occult blood.mp.
54 faecal occult blood.mp.
55 (fob or fobt).mp.
56 Carcinoembryonic Antigen/
57 Carcinoembryonic Antigen.tw.
58 Carcinogenic embryonic Antigen.tw.
59 cea.tw.
60 Colonography, computed tomographic/
61 (ct scan adj2 abdom$).tw.
62 virtual colography.mp.
63 virtual colonography.mp.
64 virtual colonoscopy.mp.
65 Proctoscopy/ or proctoscopy.mp.
66 anoscopy.mp.
67 Sigmoidoscopy/ or sigmoidoscopy.mp.
68 barium enema.mp.
69 ultrasound.mp. or Endosonography/
70 Digital rectal examination/
71 ((per rect$ or pr) adj exam$).tw.
72 or/44-71
73 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/
74 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw.
75 73 or 74
76 27 or 43
77 75 and 72 and 76
78 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ed.
79 77 and 78

Database: EMBASE
Search Strategy:
---
1 exp Primary health care/
2 general practitioner/
3 ((family or general) adj practitioner$).mp.
4 gp.mp.
5 Family physician/
6 family physician$.mp.
7 family doctor$.mp.
8 general practice/
9 ((family or general) adj practice$).mp.
10 primary care.mp.
11 primary health care.mp.
12 or/1-11
13 Meta Analysis/
14 "systematic review"/
15 (meta-analy$ or metaanaly$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
16 (systematic adj (review$ or overview$)).mp.
17 review.pt.

18 review.ti.
19 or/13-18
20 letter.pt.
21 editorial.pt.
22 or/20-21
23 19 not 22
24 "sensitivity and specificity"/
25 sensitivity.tw.
26 specificity.tw.
27 "prediction and forecasting"/
28 predictive value$.tw.
29 predictive value$ of test$.tw.
30 roc curve/
31 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw.
32 exp diagnostic error/
33 (false adj (positive or negative)).tw.
34 diagnostic accuracy/
35 accuracy.tw.
36 reference value/
37 reference value$.tw.
38 likelihood ratio$.tw.
39 ((pre-test or pretest) adj probability).tw.
40 post-test probability.tw.
41 differential diagnosis/
42 or/24-41
43 exp blood cell count/
44 (CBC or FBC or full blood count).tw.
45 c-reactive protein.mp. or C Reactive Protein/
46 erythrocyte sedimentation rate/
47 erythrocyte sedimentation rate.mp.
48 ferritin.tw. or Ferritin blood level/ or Ferritin/
49 serum iron.mp. or exp Iron Blood Level/
50 occult blood/
51 faecal occult blood.tw.
52 (fob or fobt).tw.
53 Carcinoembryonic Antigen.tw.
54 Carcinogenic embryonic Antigen.tw.
55 Carcinoembryonic Antigen/
56 CEA.tw.
57 virtual colography.tw.
58 virtual colonography.mp.
59 virtual colonoscopy.mp.
60 computer assisted tomography/
61 computed tomographic colonography/
62 (ct scan adj2 abdom$).tw.
63 barium enema.mp. or Barium Enema/
64 Rectoscopy/ or proctoscopy.tw.
65 anoscopy/ or anoscopy.mp.
66 Ultrasound/ or ultrasound.mp.
67 Sigmoidoscopy/ or sigmoidoscopy.tw.
68 Digital rectal examination/
69 pr exam$.tw.
70 per rectum exam$.tw.
71 or/43-70

72 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp intestine cancer/ or exp intestine tumor/
73 exp Abdominal Tumor/
74 72 or 73
75 42 or 23
76 74 and 75 and 71
77 limit 76 to (human and english language)
78 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ew.
79 77 and 78

For Question 3 (Risk factors)

Database: Ovid MEDLINE(R)

Search Strategy:

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1 exp colorectal neoplasms/
2 exp large intestine tumor/
3 ((proximal or ascending or descending or transverse) adj colon adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
4 ((colon$ or colorect$ or bowel$ or large bowel$ or intestin$ or pelv$ or abdom$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
5 ((sigmoid$ or rectosigmoid$ or jejunum or ileum or ileal or cecum or cecal or ileocecal or ileocecal junction or ICJ or appendi$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
6 CRC.tw.
7 Burkitt$ lymph$.tw.
8 (hereditary nonpolyposis colon cancer or nonpolyposis colon cancer or HNPCC or Lynch$ syndrome).tw.
9 exp primary health care/
10 (primary care or primary health care).tw.
11 Family Practice/
12 Physicians, Family/
13 (family practi$ or family doctor$ or family physician$ or gp$ or general practi$).tw.
14 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ed.
15 meta-analysis.pt,sh.
16 (meta-anal$ or metaanal$).tw.
17 (quantitativ$ review$ or quantitativ$ overview$).tw.
18 (systematic$ review$ or systematic$ overview$).tw.
19 (methodologic$ review$ or methodologic$ overview$).tw.
20 (integrative research review$ or research integration$).tw.
21 quantitativ$ synthes$.tw.
22 (medline or medlars).tw,sh. or embase.tw.
23 (scisearch or psychinfo or psycinfo).tw.
24 (psychlit or psyclit).tw.
25 (hand search$ or manual search$).tw.
26 (electronic database$ or bibliographic database$).tw.
27 (pooling or pooled analys$ or mantel haenszel).tw.
28 (peto or der simonian or dersimonian or fixed effect$).tw.
29 review.pt,sh. or review$.tw. or overview$.tw.
30 or/9-13
31 or/22-28
32 or/15-21
33 29 and 31

34 32 or 33
35 or/1-8
36 35 and 34
37 limit 36 to english language
38 limit 37 to humans
39 38 and 14
40 remove duplicates from 39

Database: EMBASE
Search Strategy:
---
1 exp colorectal neoplasms/
2 exp large intestine tumor/
3 ((proximal or ascending or descending or transverse) adj colon adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
4 ((colon$ or colorect$ or bowel$ or large bowel$ or intestin$ or pelv$ or abdom$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
5 ((sigmoid$ or rectosigmoid$ or jejunum or ileum or ileal or cecum or cecal or ileocecal or ileocecal junction or ICJ or appendi$) adj3 (cancer$ or neoplas$ or tumour$ or tumor$ or carcino$ or malignan$)).tw.
6 CRC.tw.
7 Burkitt$ lymph$.tw.
8 (hereditary nonpolyposis colon cancer or nonpolyposis colon cancer or HNPCC or Lynch$ syndrome).tw.
9 exp primary health care/
10 (primary care or primary health care).tw.
11 Family Practice/
12 Physicians, Family/
13 (family practi$ or family doctor$ or family physician$ or gp$ or general practi$).tw.
14 meta-analysis.pt,sh.
15 (meta-anal$ or metaanal$).tw.
16 (quantitativ$ review$ or quantitativ$ overview$).tw.
17 (systematic$ review$ or systematic$ overview$).tw.
18 (methodologic$ review$ or methodologic$ overview$).tw.
19 (integrative research review$ or research integration$).tw.
20 quantitativ$ synthes$.tw.
21 (medline or medlars).tw,sh. or embase.tw.
22 (scisearch or psychinfo or psycinfo).tw.
23 (psychlit or psyclit).tw.
24 (hand search$ or manual search$).tw.
25 (electronic database$ or bibliographic database$).tw.
26 (pooling or pooled analys$ or mantel haenszel).tw.
27 (peto or der simonian or dersimonian or fixed effect$).tw.
28 review.pt,sh. or review$.tw. or overview$.tw.
29 or/9-13
30 or/21-27
31 or/14-20
32 28 and 30
33 31 or 32
34 or/1-8
35 34 and 33
36 limit 35 to english language
37 limit 36 to humans

38 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ew.
39 38 and 37

For Question 4 (Delay)
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp abdominal neoplasms/ or anal gland neoplasms/ or digestive system neoplasms/ or gastrointestinal neoplasms/ or gastrointestinal stromal tumors/ or exp intestinal neoplasms/ or peritoneal neoplasms/ or pelvic neoplasms/
2 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw.
3 or/1-2
4 (delay$ adj3 practitioner$).tw.
5 (delay$ adj3 diagnos$).tw.
6 (delay$ adj3 patient$).tw.
7 (diagnos$ adj1 delay$).tw.
8 (diagnos$ adj earl$).tw.
9 early diagnosis/
10 earl$ diagnosis.tw.
11 (earl$ adj detect$).tw.
12 (earl$ adj present$).tw.
13 (earl$ adj symptom$).tw.
14 exp health behavior/
15 exp attitude to health/
16 Physician-patient relations/
17 or/4-16
18 "referral and consultation"/
19 referral$.tw.
20 (late$ adj refer$).tw.
21 (earl$ adj refer$).tw.
22 Disease progression/
23 Time factors/
24 Physician's practice patterns/
25 or/18-24
26 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ed.
27 3 and 17 and 25 and 26
28 limit 27 to (english language and humans)

Database: EMBASE
Search Strategy:
---
1 digestive system tumor/ or gastrointestinal stromal tumor/ or gastrointestinal tumor/ or digestive system cancer/ or exp intestine cancer/ or exp intestine tumor/
2 ((rect$ or colorectal$ or alimentary or colon$ or gallbladder$ or duoden$ or gastrointestin$ or anal or intestin$ or liver or digestive or abdom$) adj2 (tumor$ or tumour$ or cancer$ or neoplasm$ or carcinoma$)).tw.
3 or/1-2
4 Cancer diagnosis/
5 early diagnosis/

6 (earl$ adj diagnos$).tw.
7 diagnos$ earl$.tw.
8 Delayed Diagnosis/
9 (delay$ adj3 diagnos$).tw.
10 (diagnos$ adj1 delay$).tw.
11 (delay$ adj3 practitioner$).tw.
12 Patient attitude/
13 Attitude to health/ or Attitude to illness/ or Illness behavior/
14 (delay$ adj3 patient$).tw.
15 earl$ detection.tw.
16 (detect$ adj earl$).tw.
17 (earl$ adj present).tw.
18 (earl$ adj symptom$).tw.
19 or/4-18
20 patient referral/
21 referral$.tw.
22 (earl$ adj refer$).tw.
23 (late$ adj refer$).tw.
24 Time factors/
25 exp disease course/
26 25 and (5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 22 or 23)
27 clinical practice/
28 or/20-24,26-27
29 3 and 19 and 28
30 (200906: or 200907: or 200908: or 200909: or 200910: or 200911: or 200912: or 2010: or 2011: or 2012: or 2013: or 2014: or 2015:).ew.
31 29 and 30
32 limit 31 to (human and english language)

OUTCOMES DEFINITION

1. **EDUCATION AND INFORMATION** – EDUCATION AND INFORMATION means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "EDUCATION AND INFORMATION."

2. **ENDORSED** – ENDORSED means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.