



Evidence-Based Series #15-6: Section 1

Gastroscopy Following a Positive Fecal Occult Blood Test and Negative Colonoscopy: Guideline Recommendations

J. Allard, R. Cosby, M.E. Del Giudice, E.J. Irvine, D. Morgan, and J. Tinmouth

A Quality Initiative of the Upper GI Screening Panel and the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 30, 2009

The full Evidence-based Series #15-6 is comprised of 3 sections and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Cancer Screening page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/screening-eps/>

Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

QUESTION

Should gastroscopy for upper gastrointestinal (UGI) cancer be performed for patients with a positive fecal occult blood test (FOBT) and negative colonoscopy who are participating in a population-based colorectal cancer (CRC) screening program?

TARGET POPULATION

This guideline is targeted toward men and women who participate in a CRC screening program and have had a positive FOBT followed by colonoscopy without identifiable colonic lesions to account for their positive FOBT.

INTENDED USERS

The intended users of this guidance document are health professionals involved in the screening, diagnosis, treatment, and follow up of persons enrolled in a population-based CRC screening program. This may include gastroenterologists, family physicians, surgeons, and other health care professionals.

RECOMMENDATIONS AND KEY EVIDENCE

Recommendation

The current body of evidence is insufficient to recommend for or against, in a population-based CRC screening program, routine esophagogastroduodenoscopy (EGD) in FOBT positive/colonoscopy negative patients to detect gastric or esophageal cancers. The decision to undertake an EGD should be based on clinical judgement and should be individualized.

Key Evidence

- Four prospective (1-4) and five retrospective (5-9) studies of patients who were FOBT positive/colonoscopy negative and had an EGD. Of these, two studies (4,9) reported positive EGD but no information about endoscopic findings and several studies did not document the presence of anemia, upper gastrointestinal (UGI) symptoms or use of non steroidal anti-inflammatory drugs (NSAIDS).
- Based on this limited evidence, EGD had a low yield for UGI cancer, generally $\leq 1\%$, even in symptomatic or severely anemic patients. The yield for detecting non-malignant findings potentially contributing to positive FOBT was 11-21% while the yield for incidental findings unlikely contributing to positive FOBT was 10-36%. There were very few data regarding EGD results in the context of anemia or NSAIDS use.

Qualifying Statement

A recommendation regarding the use of EGD for the detection of non-cancerous pathology is not provided because it is beyond the scope of this review.

FUTURE RESEARCH

Further adequately powered studies are needed to investigate the incidence of gastric or esophageal cancer in patients, enrolled in a population based colorectal cancer screening program, who are FOBT positive and colonoscopy negative.

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EVIDENCE-BASED SERIES #15-6

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Evidence-Based Series #15-6: Section 2

Gastroscopy Following a Positive Fecal Occult Blood Test and Negative Colonoscopy: Evidentiary Base

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Report Date: March 30, 2009

QUESTION

Should gastroscopy for upper gastrointestinal (UGI) cancer be performed for patients with a positive fecal occult blood test (FOBT) and negative colonoscopy, who are participating in a population-based colorectal cancer (CRC) screening program?

INTRODUCTION

In Canada, CRC is the fourth most commonly diagnosed cancer and the second leading cause of cancer death, with an estimated 21,500 new cases and 8900 deaths in 2008. In Ontario, there will be an estimated 8000 new cases and 3250 deaths in 2008 (1). If CRC is detected early, the five-year survival rate is 93.2%, whereas the five-year survival rate for those with metastatic disease is only 8.1% (2). Most early colorectal cancers are asymptomatic, and population screening has been shown to be an effective strategy in significantly reducing mortality rates (3-6). To this end, a colorectal cancer screening program, ColonCancerCheck (<http://www.coloncancercheck.ca/>), was launched in the province of Ontario in 2008. Through this program, average-risk adults, defined as those individuals who are asymptomatic, at least 50 years of age, and without any first-degree relatives with a history of CRC, are screened with FOBT. Any individual testing positive for fecal occult blood is then referred to a specialist for colonoscopy.

A sizeable number of those with a positive FOBT will not have any identifiable lesion found at colonoscopy to account for their positive FOBT screen (7). Results of a pilot CRC screening program in the United Kingdom (UK) indicates that 1.9% of those screened for CRC will be FOBT positive, and 53% of those will have a negative colonoscopy (8). Therefore, approximately 1% of those who presented for CRC population screening were FOBT positive and colonoscopy negative in the UK experience. Results from a French CRC screening program indicates that 2.6% of those screened were FOBT positive, and 37% of these people had a negative colonoscopy (9). While some of these cases may be attributable to false-positive FOBT, it is reasonable to assume that other cases may be attributable to blood loss

from upper gastrointestinal (UGI) or small bowel lesions including, but not limited to, possible malignancies. Diagnosis of these lesions would require further investigation. At present, some FOBT-positive/colonoscopy-negative patients are referred for UGI investigations, and others are not. Some of the negative colonoscopy investigations might also be owing to false-negative tests in up to 5.9% (10). Currently there is a lack of consensus about whether or not upper GI investigation by esophagogastroduodenoscopy (EGD) is routinely warranted in such cases. The use of EGD under these circumstances might add more pressure on limited endoscopy resources.

The purpose of this systematic review is to evaluate the evidence concerning the use of routine EGD to detect UGI cancers in patients participating in a population-based CRC screening program who are FOBT positive and colonoscopy negative.

METHODS

The evidence-based series (EBS) guidelines, developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC), use the methods of the Practice Guidelines Development Cycle (11). To answer the question posed above, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected by one methodologist (RC) and reviewed by two members of the PEBC Upper Gastrointestinal (GI) Screening Panel (JA and EJI). The reference lists from those sources were also searched for additional trials.

This systematic review is a convenient and up-to-date source of the best available evidence examining UGI endoscopic screening subsequent to a positive FOBT and negative colonoscopy. The body of evidence in this review is comprised primarily of prospective and retrospective cohort and cross-sectional studies that have evaluated the role of UGI investigation in FOBT-positive/colonoscopy-negative patients. That evidence forms the basis of the recommendations developed by the Upper GI Screening Panel (Appendix 1). 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

The MEDLINE (1990 through May [week one] 2008) and EMBASE (1990 through week 20 2008) databases were searched for relevant publications, using search terms pertaining to colonoscopy, gastroscopy, and gastrointestinal neoplasms. Several key papers were indexed using very different terms, and therefore the search strategies were modified and repeated in an effort to capture the relevant literature. The full MEDLINE and EMBASE literature search strategies can be found in Appendices 2 and 3, respectively. The starting date of the search was 1990 as this is when evidence regarding screening began to appear in the literature.

Environmental Scan

An environmental scan was conducted in May 2008 to locate published and unpublished documents outside the indexed literature. Documents pertaining to UGI screening for those patients who are colonoscopy negative following a positive FOBT in a population-based CRC screening program from Canada and health care organizations in the USA, UK, Australia, and New Zealand were searched. For a complete list of websites searched, please refer to Appendix 4.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in the systematic review if they were published English-language reports involving human participants, including practice guidelines, systematic reviews (with or without meta-analyses), and all publication types, except those listed in the exclusion criteria, that examined the role of UGI screening in patients who had a negative colonoscopy following a positive FOBT.

If an EGD was not performed after a negative colonoscopy and patients were followed to determine a new occurrence of UGI cancer, the studies involved were included only if they reported cases of UGI cancers occurring within three years of the positive FOBT. Three years was chosen based on the mean sojourn time for CRC (the time between an undetectable preclinical screening and the clinical phase) that has been reported to be 2.8 years in a Taiwanese study (12) and 2.6 years in a French study (13).

In theory, population screening should include only asymptomatic participants, but in practice, some people presenting for screening will be symptomatic, which realistically reflects medical practice. For this reason, papers dealing with either symptomatic or asymptomatic patients were retained. At a minimum, a group of FOBT-positive/colonoscopy-negative patients had to be identified in the paper.

Exclusion Criteria

Letters, editorials, notes, case-reports, commentaries, and non-systematic reviews were not included in the systematic review.

Synthesizing the Evidence

There was considerable heterogeneity in the design methodology of the studies selected and outcomes reported; this, together with a lack of fully published randomized controlled trials (RCTs), did not support pooling data using meta-analytic techniques.

RESULTS

Literature Search Results

The MEDLINE search yielded 439 hits, 36 of which were potentially relevant and ordered for full review; five met selection criteria and were retained. The EMBASE search yielded 1119 hits, of which 34 were potentially relevant, excluding duplicates from the MEDLINE search (Table 1); three met selection criteria and were retained. A search of the reference lists of included studies yielded 14 hits, of which one was retained. A flow diagram illustrating the literature search results can be found in Appendix 5.

Table 1. Literature search results.

Date	Database	Dates Searched	Hits	Ordered for Full Article Review
May 16, 2008	MEDLINE	1990 - May (week 1) 2008	439	36
May 16, 2008	EMBASE	1990 - Week 20 2008	1119	34

Environmental Scan Results

The environmental scan did not yield any papers, documents, or guidance pertaining to the use of UGI investigations in patients who have a positive FOBT followed by a negative colonoscopy.

Study Characteristics and Quality

Five studies were identified that examined the occurrence of gastric cancer following a negative colonoscopy in patients who had positive FOBTs (7,14-17). Of these, two were studies in which patients were originally part of a population screening program for CRC (7,14). Participants in the Thomas and Hardcastle (14) study who were FOBT positive/colonoscopy negative and were subsequently noted to be symptomatic received EGD, and the outcomes for this small group of patients (n=14) were reported. Zappa et al. (7) identified a large group of FOBT-positive/colonoscopy-negative patients and did not undertake EGD but did follow up using database linkage procedures. As they reported the number of GI cancers that occurred within a three-year follow-up period, they are included in this report. The remaining three studies were prospective (15) and retrospective (16,17) studies in which all FOBT-positive /colonoscopy-negative patients were assessed by EGD for gastric cancer.

Four studies were identified that examined the diagnosis of gastric cancer in patients who had same-day EGD and colonoscopy after a positive FOBT; in these studies a subgroup of colonoscopy-negative patients could be identified (18-21). Two studies collected data prospectively (18,21), and two studies collected data retrospectively (19,20). Participants in all four studies underwent bidirectional endoscopy. The order of endoscopy was either colonoscopy followed by EGD (20,21), EGD followed by colonoscopy (19), or as determined by institutional availability (18). As the outcomes related to the subgroup of FOBT-positive/colonoscopy-negative patients were not reported separately in two of these four studies (18,19,21), only limited information could be obtained from these articles. Please refer to Table 2 for a summary of each study.

Five studies used a guaiac FOB test only (15,16,18,20,21), two studies used both a guaiac and an immunochemical FOB test, with patients being tested with a guaiac test until 1995 and with an immunochemical test after 1995 in one study (7) and with one or the other, or both tests in some cases, in the other study (14). Two studies did not report the type of FOB test used (17,19). Three studies did not rehydrate samples (14,18,20). The remaining studies did not report whether or not samples were rehydrated.

Measures of study quality included reporting conflicts of interest and identification of sources of funding. Only Hisamuddin et al. (20) reported specifically on authors' conflict of interest and indicated that they had no conflicts. No other papers reported on conflict of interest. Information regarding source of funding was not reported in any of these studies.

Table 2: Summary of studies of FOBT-positive/colonoscopy-negative patients or studies with an identifiable FOBT-positive/colonoscopy-negative subgroup of patients.

Study (Reference)	Type of Study	Study Details	Type of FOBT Used	Guaiac Samples - Rehydrated or Not Rehydrated	N (FOBT Pos/Col Neg)
Thomas & Hardcastle, 1990 (14)	Prospective	-asymptomatic patients randomized to CRC screening with FOBT or control group (received no screening) -FOBT+ patients underwent colonoscopy or flexible sigmoidoscopy combined with double contrast barium enema - EGD done on those FOBT pos/COL neg patients who were subsequently deemed to be symptomatic	Guaiac and/or immuno-chemical	Not Rehydrated	14
Hsia & Al-Kawas, 1992 (15)	Prospective	-asymptomatic FOBT pos/COL neg patients referred for upper endoscopy	Guaiac	NR	70
Chen et al. 1993 (16)	Retrospective	-FOBT pos/COL neg patient who were asymptomatic, symptomatic, anemic or had incomplete documentation and were referred for upper endoscopy	Guaiac	NR	211
Bini et al. 1999 (17)	Retrospective	-asymptomatic FOBT pos/COL neg patients who underwent upper endoscopy	NR	NR	498
Zappa et al. 2007 (7)	Retrospective	-patients attending for FOBT screening identified from a screening database -FOBT pos patients underwent colonoscopy - authors report on a FOBT pos/COL neg subgroup - EGD not done but patients followed up through databases and registries -authors report the number of UGI cancers in the first 3 years after FOBT pos	Guaiac or immuno-chemical	NR	3555
Hisamuddin et al. 2006 (20)	Retrospective	-FOBT pos patients who underwent same day bidirectional endoscopy -sequence was colonoscopy followed by EGD -authors report outcomes from a FOBT pos/COL neg subgroup	Guaiac	Not Rehydrated	70
Zuckerman & Benitez, 1992 (18)	Prospective	-FOBT pos or iron deficiency anemia patients who underwent bidirectional endoscopy -sequence dependent on scheduling and could be separated by up to 14 days - authors identify a group of FOBT pos/COL neg patients but do not report separate outcomes for this subgroup	Guaiac	Not Rehydrated	74
Ali et al. 2003 (19)	Retrospective	-FOBT pos patients underwent same day bidirectional endoscopy -sequence was EGD followed by colonoscopy in 85% of cases - authors identify a group of FOBT pos/COL neg patients but do not report separate outcomes for this subgroup	NR	NR	125
Stray & Weberg, 2006 (21)	Prospective	-FOBT pos patients with or without iron deficient anemia, solely iron deficiency anemia or solely iron deficiency and underwent same day bidirectional endoscopy -sequence was colonoscopy followed by EGD - authors identify a group of FOBT pos/COL neg patients but do not report separate outcomes for this subgroup	Guaiac	NR	146

COL neg=colonoscopy negative; CRC = colorectal cancer; EGD = esophagogastroduodenoscopy; FOBT pos=fecal occult blood test positive; N=number of patients; NR=not reported;

Outcomes

Cancer Outcomes

Nine studies identified a group of patients who were FOBT positive/colonoscopy negative (Table 3). Some studies were limited to patients who were either symptomatic (14) or asymptomatic (15,17), others included both symptomatic and asymptomatic patients (16,18,20), and several studies did not report whether patients were symptomatic or not (7,19,21). Chen et al. (16) categorized their patients into four groups: asymptomatic, symptomatic, severely anemic (which included those who were both symptomatic and severely anemic), and 'incomplete,' which was a group of patients with incomplete documentation with respect to anemia and/or symptoms. One study did not provide a definition of 'symptomatic' (20). In all other studies that included symptomatic patients, symptomatic was defined as including dyspepsia as well a subset of the following: dysphagia, heartburn, abdominal pain, nausea, vomiting, weight loss, and diarrhea (14,16,18). One study (20) reported that patients had to have at least one positive window to be considered FOBT positive. No other studies reported how many windows had to be positive for a patient to be considered FOBT positive.

Eight of the studies performed EGD on all FOBT-positive/colonoscopy-negative patients (14-21), whereas one study (7) conducted a large retrospective cohort study of patients who were followed through a cancer registry linkage. Rates of positive findings (not limited to cancers) at EGD ranged from a low of 13% (19) to a high of 43% (14). Of note, this latter study is a report of a very small subgroup (n=14) of symptomatic patients.

Three studies (15,16,20) found no cases of UGI cancer, defined as either gastric or esophageal cancer. Four studies reported cases of UGI cancer. Thomas and Hardcastle (14) found only one case of gastric cancer in their small subgroup of 14 symptomatic FOBT-positive/colonoscopy-negative patients. Bini et al. (17) found five cases of UGI cancer (four gastric and one esophageal) in their study of 498 asymptomatic patients, and Zappa et al. (7) found 14 cases of gastric cancer between 0-35 months following a positive FOBT (unknown if patients were symptomatic or not). Zuckerman and Benitez (18) found one case of UGI cancer in their study of 74 asymptomatic and symptomatic FOBT-positive/colonoscopy-negative patients. This represents 1% or less of the total population studied. The final two studies (19,21) did not provide outcome information that could be specifically related to the FOBT-positive/colonoscopy-negative subgroup. Therefore, no conclusion can be drawn regarding the UGI cancer yield in these studies.

Probable Upper Gastrointestinal Contributors to Positive FOBT

Five studies reported outcomes other than UGI cancer outcomes (Table 3). The Panel divided these other non-cancer outcomes into two groups: probable UGI contributors to a positive FOBT and probable UGI incidental finding. Probable UGI contributors include peptic ulcer disease (stomach, esophagus, and duodenum) esophagitis, vascular malformations, and gastric polyps (>1 cm). One study of symptomatic patients reported no probable contributors (14). Among other symptomatic patients (including those with severe anemia), 11-21% had a probable UGI contributor to a positive FOBT (16), whereas 7-19% of asymptomatic patients had a probable contributor (15-17). Hisamuddin et al. (20) had both asymptomatic and symptomatic patients in their study and reported that 16% of this aggregate group had a probable contributor.

None of the remaining four studies one (7,18,19,21) reported on non-cancer outcomes separately for their FOBT-positive/colonoscopy-negative subgroups.

Probable Upper Gastrointestinal Incidental Findings

Probable UGI incidental findings include Barrett’s esophagus, gastric and duodenal erosions, duodenitis, jejunitis, esophageal and gastric varices, esophageal stricture, duodenal adenoma, non-erosive esophagitis, benign gastroduodenal disease, and small gastric polyps (< 1 cm). Among symptomatic patients (including those with severe anemia in one study), 24% to 36% had a probable UGI incidental finding at EGD (14,16) while 10-36% of asymptomatic patients had a probable incidental finding (15-17). Hisamuddin et al. (20) had both asymptomatic and symptomatic patients in their study and reported that 20% of this aggregate group had a probable incidental finding.

None of the other four studies one (7,18,19,21) reported on non-cancerous outcomes separately for their FOBT-positive/colonoscopy-negative subgroups.

Table 3. Upper gastrointestinal outcomes in FOBT-positive/colonoscopy-negative patients who underwent esophagogastroduodenoscopy.

Study (Reference)	Type of Study	Groups	N	EGD Positive	UGI Cancer ^a	Probable UGI Contributor To Positive FOBT ^b	Probable UGI Incidental Finding ^c
Thomas & Hardcastle, 1990 (14)	P	Symptomatic	14	6(43%)	1(7%)	0	5(36%)
Hsia & Al-Kawas, 1992 (15)	P	Asymptomatic	70	19(27%)	0	13(19%) ^e	7(10%) ^e
Chen et al. 1993 (16)	R	Asymptomatic	117	50(43%)	0	8(7%)	42(36%)
		Symptomatic	37	13(35%)	0	4(11%)	9(24%)
		Severely Anemic	33	15(45%)	0	7(21%)	8(24%)
		Incomplete (uk)	24	10(42%)	0	5(21%)	5(21%)
		Total	211	88(42%)	0	24(11%)	64(30%)
Bini et al. 1999 (17)	R	Asymptomatic	498	141(28%)	5(1%)	66(13%)	70(14%)
Zappa et al. 2007 (7)	R	Unknown	3555	NA ^d	14(<1%) ^f	NR	NR
Hisamuddin et al. 2006 (20)	R	Asymptomatic & Symptomatic	70	25(36%)	0	11(16%)	14(20%)
Zuckerman & Benitez, 1992 (18)	P	Asymptomatic & Symptomatic	74	27(36%)	1(1%)	NR	NR
Ali et al. 2003 (19)	R	Unknown	125	16(13%)	NR	NR	NR
Stray & Weberg, 2006 (21)	P	Unknown	146	37(25%)	NR	NR	NR

EGD=esophagogastroduodenoscopy; FOBT=fecal occult blood test; NA=not applicable; NR=not reported; P=prospective; R=retrospective; UGI=upper gastrointestinal; uk=unknown

^aIncludes gastric and esophageal cancers.

^bIncludes peptic ulcer disease, esophagitis, vascular malformations and gastric polyps (>1 cm).

^cIncludes Barrett’s esophagus, gastric and duodenal erosions, gastritis, duodenitis, jejunitis, esophageal and gastric varices, esophageal stricture, duodenal adenoma, non-erosive esophagitis, benign gastroduodenal disease, and small gastric polyps (<1cm).

^dEGD not done. Patients followed through registries and databases.

^eThese numbers add up to 20 instead of 19 because one patient had both a probable contributor to their positive FOBT and a probable incidental finding

^fUGI cancers occurring within 35 months of positive FOBT.

Effect of Anemia

There were few data from these studies that also examined anemia as a possible predictor of EGD results (in addition to positive FOBT and negative colonoscopy). Furthermore, the outcomes reported differ among studies and could not be combined.

Effect of NSAID Use

There were few data from these studies that also looked at aspirin or NSAID use as a possible predictor of EGD results (in addition to positive FOBT and negative colonoscopy). Furthermore the outcomes reported differ among studies and could not be combined.

DISCUSSION

The current management of patients who undergo screening for CRC and who test FOBT positive and colonoscopy negative is inconsistent. As a greater proportion of the population complies with guidelines for CRC screening, there will be an increasing and perhaps substantial number of such patients who fall into this category. However, there are relatively few studies that have fully addressed whether EGD is warranted in this situation using sound study design and appropriate outcome assessment. The evidence base compiled for this document consists of four prospective and five retrospective studies. Two of these studies (19,21) only identified a group of FOBT-positive/colonoscopy-negative patients with a positive EGD, but provided no information about the endoscopic findings, making the results uninterpretable. The current document does not address the entire issue of how to manage FOBT-positive/colonoscopy-negative patients but examines whether or not EGD is warranted, to detect UGI cancer, in this group of patients.

In the remaining seven studies, the prevalence of UGI cancer was very low. Three studies (15,16,20) found no UGI cancers. Three studies (7,17,18) observed 1% or less UGI cancers, and one study (14) noted 7% UGI cancers, representing one case out of 14 symptomatic patients. It should be noted that while a 1% yield of UGI cancers may seem comparable to the yield of colon cancers detected at screening colonoscopy, the quality of the studies evaluating EGD is not as good as those evaluating CRC screening. The gastroscopy studies contain heterogeneous samples that are not truly representative of a screening population and the number of patients evaluated is small in comparison to the numbers evaluated in CRC screening studies.

Diagnostic findings at EGD other than UGI cancer were more prevalent. Overall, a probable UGI contributor to the positive FOBT was reported in 7-21% of FOBT-positive/colonoscopy-negative patients. Probable contributors were defined as peptic ulcer disease, esophagitis, vascular malformations, and gastric polyps (>1cm). It was not really known if gastric polyps greater than 1 cm would cause a positive FOBT. These larger gastric polyps were only reported in two studies (17,20), and their inclusion as a probable UGI contributor to a positive FOBT did not change any conclusions of this report. The proportion of cases with findings that were reported as likely to be incidental (and unlikely to account for a positive FOBT) occurred in 10-36% of patients. These incidental findings included Barrett's esophagus, gastric and duodenal erosions, gastritis, duodenitis, jejunitis, esophageal and gastric varices, esophageal stricture, duodenal adenoma, benign gastroduodenal disease, and gastric polyps. The variability in the descriptions of UGI lesions other than cancer is likely owing to the variations between studies in defining what constitutes a positive EGD.

There were very few data reported regarding EGD results and the presence or absence of anemia and even fewer data regarding EGD and NSAID use. Moreover, the papers that did report on these variables all reported different outcomes. As most patients who undergo screening are over the age of 50, many will be taking aspirin for cardiovascular disease prevention and/or NSAIDs for arthritis and analgesia. In addition, anemic patients are unique and do not fall under the auspices of screening programs. They have a red flag which requires further investigation. These two groups of patients would benefit from further study as separate subgroups.

The body of literature examining the controversial issue of performing routine EGD in FOBT-positive/colonoscopy-negative patients is sparse. The data gathered from the studies in

this systematic review suggest that the number of UGI cancers found in FOBT-positive/colonoscopy-negative patients is small, in the order of 1% or less, although the rate of other UGI findings was higher. However, even though the risk associated with EGD is small, in the order of 0.03% for perforation (22,23), other factors related to the cost and endoscopic resources are significant, considering the potential numbers of patients who will emerge from CRC screening programs with a positive FOBT and a negative colonoscopy. Performing routine EGD in these patients would significantly add to the cost of screening programs while potentially adding little value with respect to effectiveness of screening for UGI cancer.

CONCLUSION

The current body of evidence is insufficient to recommend for or against, in a population-based CRC screening program, routine EGD in FOBT-positive/colonoscopy-negative patients to detect gastric or esophageal cancers. The decision to undertake an EGD should be based on clinical judgement and should be individualized.

Further adequately powered studies are needed to investigate the incidence of gastric or esophageal cancer in patients enrolled in a population-based CRC screening program who are FOBT positive and colonoscopy negative.

CONFLICT OF INTEREST

All authors report no conflicts of interest.

JOURNAL REFERENCE

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EVIDENCE-BASED SERIES #15-6

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Appendix 2. MEDLINE search strategy.

Search 1

1. Colorectal neoplasms/di
2. exp Colonoscopy/
3. 1 or 2
4. Digestive System Diseases/di
5. Gastrointestinal neoplasms/di
6. Gastrointestinal diseases/di
7. Stomach ulcer/di
8. Stomach neoplasms/di
9. Peptic ulcer/di
10. Peptic ulcer hemorrhage/di
11. Liver disease/di
12. or/4-11
13. exp Mass Screening/
14. 3 and 12
15. limit 14 to english language
16. limit 15 to yr="1990 - 2008"
17. from 16 keep 7,18,22,38,48,58,67-68,78-79,99,101-102,138,143,153
18. 3 and 12 and 13
19. limit 18 to english language
20. limit 19 to yr="1990 - 2008"

Search 2

1. exp Gastroscopy/
2. Esophagogastroduodenscopy.mp.
3. exp Endoscopy/ or exp Endoscopy, Gastrointestinal/ or exp Endoscopy, Digestive System/
4. 1 or 2 or 3
5. Gastrointestinal neoplasms/di
6. Gastrointestinal diseases/di
7. Stomach ulcer/di
8. Stomach neoplasms/di
9. peptic ulcer/di
10. peptic ulcer hemorrhage/di
11. Liver diseases/di
12. or/5-11
13. exp Mass Screening/
14. 4 and 12 and 13
15. limit 14 to english language
16. limit 15 to yr="1990 - 2008"
17. from 16 keep 5-6,10-11,13,16,22,44,49,51,59

Search 3

1. exp Gastroscopy/
2. Esophagogastroduodenoscopy.mp. or exp Endoscopy, Digestive System/
3. 1 or 2
4. exp Gastrointestinal Neoplasms/
5. exp Gastrointestinal Diseases/
6. exp Stomach Ulcer/
7. exp Stomach Neoplasms/
8. exp Peptic Ulcer/
9. exp Peptic Ulcer Hemorrhage/
10. Liver disease/di
11. or/4-10
12. exp Mass Screening/
13. 3 and 11 and 12
14. exp Colorectal Neoplasms/
15. 13 not 14
16. limit 15 to english language
17. limit 16 to yr="1990 - 2008"
18. from 17 keep 47,53,63,86,127,133,156,159,180

Appendix 3. EMBASE search strategy.

Search 1

1. Colorectal cancer/di
2. exp COLONOSCOPY/
3. exp Cancer Screening/
4. exp Occult Blood/
5. exp GASTROSCOPY/
6. exp ESOPHAGOGASTRODUODENOSCOPY/
7. exp Gastrointestinal Endoscopy/
8. Digestive system cancer/di
9. Stomach ulcer/di
10. Stomach cancer/di
11. Upper gastrointestinal bleeding/di
12. Esophagus cancer/di
13. Peptic ulcer/di
14. Liver disease/di
15. or/5-14
16. 1 and 2 and 3 and 4 and 15
17. limit 16 to english language
18. limit 17 to yr="1990 - 2008"

Search 2

1. Colorectal cancer/di
2. exp COLONOSCOPY/
3. 1 or 2
4. Digestive System Cancer/di
5. gastrointestinal disease/di
6. stomach ulcer/di
7. stomach cancer/di
8. upper gastrointestinal bleeding/di
9. esophagus cancer/di
10. peptic ulcer/di
11. liver disease/di
12. or/4-11
13. 3 and 12
14. limit 13 to english language
15. limit 14 to yr="1990 - 2008"

Search 3

1. exp GASTROSCOPY/
2. exp ESOPHAGOGASTRODUODENOSCOPY/
3. exp Gastrointestinal Endoscopy/
4. 1 or 2 or 3
5. Digestive System Cancer/di
6. Gastrointestinal disease/di
7. stomach ulcer/di
8. stomach cancer/di
9. Upper gastrointestinal bleeding/di
10. Esophagus cancer/di
11. Peptic ulcer/di
12. Liver disease/di
13. or/5-12
14. exp Mass Screening/
15. exp Cancer Screening/
16. 14 or 15
17. 4 and 13 and 16
18. limit 17 to english language
19. limit 18 to yr="1990 - 2008"

Appendix 4. Environmental scan.

National Guideline Clearing House
International Guideline Developers:
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

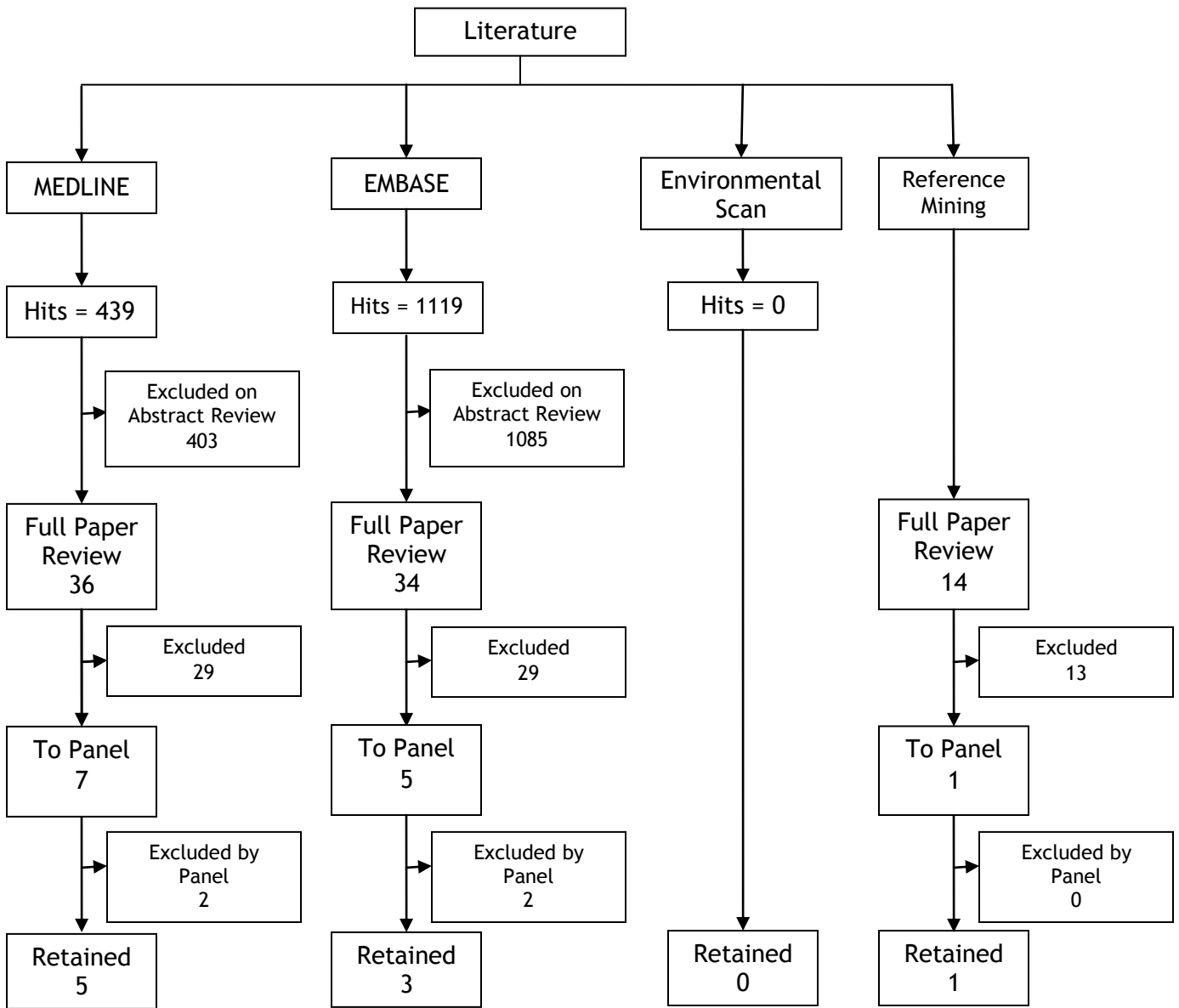
Canadian provincial cancer agencies:
BC Cancer Agency - Cancer management guidelines
Alberta Cancer Board - Treatment Guidelines
Saskatchewan Cancer Agency - Follow-up Guidelines
Cancer Care Manitoba - CCM Home
Cancer Care Nova Scotia - Guidelines

National cancer agencies (UK, AUS, NZ):
NZ Cancer Control Trust
The Cancer Council Australia
National Cancer Control Initiative (AUS)
The Collaboration for Cancer Outcomes Research and Evaluation (AUS)
State Government of Victoria, Australia
Peter MacCallum Cancer Centre (Australia)
Medical Oncology Group of Australia
Cancer UK
Cancer Services Collaborative, Avon Somerset and Wiltshire (UK)
NHS (UK)

Organizations (project specific):
Canadian Association of Gastroenterologists (CAG)
Ontario Association of Gastroenterology (OAG)
Canadian Digestive Health Foundation
American Gastroenterology Association (AGA)
British Society of Gastroenterology (BSG)
United European Gastroenterology Foundation
European Society for Primary Care Gastroenterology
American Society of Gastrointestinal Endoscopy
American College of Gastroenterology

Conferences:
Community oncology conference

Appendix 5. Flow diagram of literature search results.





Evidence-Based Series #15-6: Section 3

**Gastroscopy Following a Positive Fecal Occult Blood Test
and Negative Colonoscopy: EBS Development Methods and External
Review Process**

J. Allard, R. Cosby, M.E. Del Giudice, E.J. Irvine, D. Morgan, and J. Tinmouth

A Quality Initiative of the Upper GI Screening Panel and the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 30, 2009

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) and Guideline Development Groups (GDGs), 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 which 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 evidence-based series 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 Upper GI Screening Panel of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on gastroscopy screening following a positive FOBT and negative colonoscopy, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants by the Panel. The Panel consisted of gastroenterologists, a family physician, a methodologist, and a CCO representative (see Appendix 1 of Section 2 for a complete list).

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the RAP and their resolution by the Upper GI Screening Panel (*italicized*) included:

- It was suggested that an explicit statement articulating that the role of UGI in detecting other, non-cancerous UGI pathology was beyond the scope of this project was needed. *A Qualifying Statement following the Recommendations and Key Evidence in Section 1 was added.*
- It was suggested that, since the specific question addressed by the guideline falls into a broader management issue of patients with positive FOB testing and negative colonoscopy, a statement should be added to the Discussion acknowledging that the current guideline addresses only a portion of the overall management issue. *A clarifying sentence was added to the Discussion.*
- It was suggested that the document did not adequately describe the type of studies that were eligible for inclusion in the systematic review. *The section in the Methods describing the inclusion criteria was amended and clarified.*
- It was suggest that the section describing future studies needed to be clarified. *This section was amended.*
- Given the types of studies designs that were included in the systematic review, RAP wanted to be sure that the literature search had been done adequately such that these types of studies were adequately uncovered. *The literature search was rechecked and found to be adequate. Because publication type was not used to limit the search, all type of studies would have been found and evaluated for inclusion.*

- It was suggested that the report potentially understates the role of endoscopy in investigating those with iron-deficiency anemia and that an explicit statement indicating that these patients are unique and do not fall into the general philosophy of screening programs. *Statements were added to the Discussion that explicitly deals with this concern.*
- There were several small editorial changes suggested. *These editorial changes were made.*

Expert Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed by an Expert Panel which consisted of a group of endoscopists from the Clinical Advisory Committee of Cancer Care Ontario's Colorectal Cancer Screening Program. Key issues raised by the Expert Panel, not already covered in the RAP comments above, and their resolution by the Upper GI Screening Panel (*italicized*) included:

- It was suggested that the number of FOB positive tests (ex 1 of 3) used in each study was not reported in the guideline. *This information was obtained from each study and incorporated into the Cancer Outcomes section of Section 2.*
- It was suggested that the document should include the type of FOB test used in each study (guaiac versus immunochemical) and whether or not the samples were rehydrated or not. *This information was added to Table 2.*
- It was suggested that 2 data points were incorrect in Table 3. *These were rechecked and one data point was amended appropriately. The other data point was correct.*
- It was suggested that there was an article missing from the evidence. *The article in question was rejected by the Panel because it did not meet the inclusion criteria used for this document.*
- It was suggested that a 1% yield for detection of UGI malignancy is worth doing EGD given that the detection rate of colon cancer in CRC screening programs would be similar. *The Panel felt that the quality of the CRC screening papers was higher than the quality of the papers evaluating EGD in FOBT-positive/colonoscopy-negative patients. The papers evaluating EGD tend to be underpowered and consist of heterogeneous populations (i.e., symptomatic, asymptomatic, and anemic patients).*
- It was suggested the recommendation should be reworded such that "...the evidence is insufficient to recommend FOR OR AGAINST" routine EGD. *The recommendation was amended to incorporate the "for or against" terminology.*
- It was suggested that the document lacked an economic analysis. *An economic analysis was beyond the scope of the current document.*

External Review by Ontario Clinicians

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 review and approval of the report by the PEBC Report Approval Panel, the Upper GI Screening Panel 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 Upper GI Screening Panel.

BOX 1:

DRAFT RECOMMENDATIONS (approved for external review January 30, 2009 review)

QUESTION

Should gastroscopy for upper gastrointestinal (UGI) cancer be performed for patients with a positive fecal occult blood test (FOBT) and negative colonoscopy who are participating in a population-based colorectal cancer (CRC) screening program?

TARGET POPULATION

This guideline is targeted toward men and women who participate in a CRC screening program and have had a positive FOBT followed by colonoscopy without identifiable colonic lesions to account for their positive FOBT.

DRAFT RECOMMENDATIONS AND KEY EVIDENCE**Recommendation**

The current body of evidence is insufficient to recommend for or against, in a population-based CRC screening program, routine esophagogastroduodenoscopy (EGD) in FOBT positive/colonoscopy negative patients to detect gastric or esophageal cancers. The decision to undertake an EGD should be based on clinical judgement and should be individualized.

Key Evidence

- Four prospective (1-4) and five retrospective (5-9) studies of patients who were FOBT positive/colonoscopy negative and had an EGD. Of these, two studies (4,9) reported positive EGD but no information about endoscopic findings and several studies did not document the presence of anemia, upper gastrointestinal (UGI) symptoms or use of non steroidal anti-inflammatory drugs (NSAIDS).
- Based on this limited evidence, EGD had a low yield for UGI cancer, generally $\leq 1\%$, even in symptomatic or severely anemic patients. The yield for detecting non-malignant findings potentially contributing to positive FOBT was 11-21% while the yield for incidental findings unlikely contributing to positive FOBT was 10-36%. There were very few data regarding EGD results in the context of anemia or NSAIDS use.

Qualifying Statement

A recommendation regarding the use of EGD for the detection of non-cancerous pathology is not provided because it is beyond the scope of this review.

Methods

Targeted Peer Review: During the guideline development process, six targeted peer reviewers from Ontario, Nova Scotia, Quebec, and Alberta considered to be clinical and/or methodological experts on the topic were identified by Upper GI Screening Panel. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed, and the draft report and a questionnaire were sent via email or mail 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 January 30,

2009. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Upper GI Screening Panel 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, namely gastroenterologists, family physicians, and surgeons. 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 February 4, 2009. The consultation period ended on February 28, 2009. The Upper GI Screening Panel reviewed the results of the survey.

Results

Targeted Peer Review: Four responses were received from four reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

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

Summary of Written Comments

The main points contained in the written comments were:

1. The document lacked an economic analysis.
2. For a 1% yield for detection of UGI malignancy it may be worth doing EGD given that the detection rate of colon cancer in CRC screening programs would be similar.
3. It would be useful to know the number screened by study in Table 2.
4. The recommendation is inconclusive because of poor evidence. Could the experts go beyond the evidence to propose guidelines based on patient profile and FOBT results.

5. Consideration should be given to including a specific reference to the use of capsule endoscopy and double balloon endoscopy in the discussion.
6. It is a challenge, for many clinicians, to find the endoscopy time to perform the procedure for those patients where it is felt to be indicated based on clinical judgement.
7. There is a need to develop a meaningful prospective multicentre study that addresses the issue of FOBT positive/colonoscopy negative patients that focuses on more than UGI cancers but includes all UGI and small bowel disorders.

Professional Consultation: Five responses were received. Three respondents completed the survey and two respondents only sent back comments. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

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	
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1		2
3. I would recommend this guideline for use in practice.			1	1	1

Summary of Written Comments

The main points contained in the written comments were:

8. The lack of evidence does not really answer the question
9. The guideline should be distributed to the regional leads in Prevention and Screening, Primary Care leads and participating ColonCancerCheck hospitals.
10. It might be helpful to comment on the false negative rate of colonoscopy. This could be the cause of a negative study in the face of a positive FOBT. Many people (providers and patients alike) seem to believe that an optical examination of the colon is always accurate, which it is not.

Modifications/Actions

1. An economic analysis was beyond the scope of the current document.
2. The Panel felt that the quality of the CRC screening papers was higher than the quality of the papers evaluating EGD in FOBT-positive/colonoscopy-negative patients. The papers evaluating EGD tend to be underpowered and consist of heterogeneous populations (i.e., symptomatic, asymptomatic, and anemic patients). Since this was a comment made by several reviewers in the internal and external review process, a subsection was added to the Discussion articulating the inferior quality of the studies evaluating screening gastroscopy in comparison to the studies evaluating CRC screening.
3. Most of the studies were not screening studies.
4. Providing recommendations by going beyond the evidence would exceed the scope of what the panel was asked to do. The guideline can be updated when new evidence emerges.

5. Capsule endoscopy and double balloon endoscopy are procedures meant for patients with anemia done after a negative EDG and not for patients with a positive FOBT and fall outside the scope of the current guideline.
6. A sentence was added to the Introduction to reflect that endoscopy resources are limited.
7. A sentence was modified in the Introduction to reflect that a small bowel disorder may be the cause of fecal occult blood.
8. The evidence is what it is. The guideline can be updated when new evidence emerges.
9. CCO takes care of dissemination.
10. A sentence was added to the Introduction to state that a negative colonoscopy could be the result of a false-negative test.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Upper GI Screening Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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