14. Appropriateness of Colonoscopy: Screening for Colorectal Cancer in Asymptomatic Individuals [1]

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Introduction

Colorectal cancer is an important component of the burden of disease in developed countries because it is widespread and has a high morbidity and mortality rate [1]. In Europe, the annual age-standardized incidence (world population) of colorectal cancer is between 20 and 45 per 100 000 among males and between 15 and 30 per 100 000 among females [2]. Incidence rates increase in a regular fashion with age [2–4]. "Screening, in the context of colorectal cancer, identifies individuals who are more likely to have colorectal cancer or adenomatous polyps from among those without signs or symptoms of the disease" [1]. Screening may detect cancers at an early stage. If detected at an early stage, treatment may be curative and improve prognosis. Screening may be acceptable to many patients and generally feasible in practice.

In November 1998, a multidisciplinary European expert panel convened in Lausanne, Switzerland, to discuss and develop criteria for the appropriate use of gastrointestinal endoscopy, a widely-used procedure, regarded as highly accurate and safe. The RAND appropriateness method was chosen for this purpose, because it allows the development of appropriateness criteria based on published evidence and supplemented by explicit expert opinion. A detailed description of the RANTD appropriateness method, including the literature search process [5], and of the whole process, as well as the global results of the panel [6], are published as separate articles in the issue of the Journal. The literature review was based on a systematic search of Medline, Embase and the Cochrane Library conducted up to the end of 1997 and completed with some key articles published in 1998. Updating and revision of the literature review is currently ongoing.

This article contains three parts: 1. the review of the literature that was used by the panelists to support their ratings of appropriateness of use of colonoscopic screening for colorectal cancer in asymptomatic patients without personal history of colorectal cancer or polyps; 2. an overview of the main panel results; 3. a summary of the published evidence and of the panel based appropriateness criteria.

1. Literature Review

A general description of the epidemiology of colorectal cancer can be found in the article on surveillance after curative intent resection of a colorectal cancer published in a joint article in this issue of the Journal [7].

Screening Strategies

Although the question being examined is the appropriateness of use of colonoscopy in screening for colorectal cancer, the effectiveness of other tests for early diagnosis of colorectal cancer has also been examined (e.g. Fecal Occult Blood Test). The following literature review section consists of two parts: screening in people at average or increased risk for colorectal cancer.

Persons with Average-Risk

Fecal Occult Blood Test (FOBT)

The rationale for this examination is based on the observation that the cancerous mucosa bleeds more than normal mucosa. As polyps also bleed, particularly if they are large, and are more common than cancers, FOBT will also detect bleeding from polyps. The sensitivity is increased and the specificity decreased with rehydrated tests. The sensitivity also increases with the number of stool samples studied [1].

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Accurary of the Screening Test

A multicenter prospective study [8] analysed the accuracy of fecal occult blood screening for colorectal neoplasm and found it to be a poor indicator of the presence of neoplasm. Most cancers, and the vast majority of polyps, remained undetected. The sensitivity of Hemoccult® for colorectal cancer was 26% and, for polyps greater then 1 cm, 11–20%. The positive predictive value for cancer was about 5–8%, although the study population comprised persons with higher-than-average risk for colorectal cancer.

Another study [9] in 8104 patients from a colorectal cancer screening programme analysed three different tests: Hemoccult II®, Hemoccult IISensa® and HemeSelect® with diet. Each patient received the three tests. No rehydration was done. The main results are presented in Table **1**.

Table 1 Performance characteristics of FOBT for colorectal cancer screening [9]

	Sensitivity	Specificity	Positive predictive value
Hemoccult II	37.1 (19.7–54.6)	97.7 (97.3–98.0)	6.6 (3.7–11.2)
Hemoccult II Sensa	79.4 (64.3–94.5)	86.7 (85.9–87.4)	2.5 (1.7–3.7)
HemeSelect	68.8 (51.1–86.4)	94.4 (93.8–94.9)	5.0 (3.2–7.6)
Combination of Hemoccult II Sensa and HemeSelect	65.6 (47.6–83.6)	97.3 (96.9–97.6)	9.0 (5.8–13.6)

A guideline of the American College of Physicians [10, 11] proposed techniques for FOBT and its interpretation. In spite of the large randomized controlled trials already carried out, no consensus exists concerning such important technical issues such as diet restriction, rehydration of slides, frequency of screening, strategy for evaluating those who tested positive. Stronger evidence is available for the following technical aspects of colonoscopy: a complete colonic evaluation should be done after a positive test result because the possibility of finding an important neoplasm is high enough to warrant a work-up. Colonoscopy or flexible sigmoidoscopy plus high-quality air-contrast barium enema are both suitable methods for complete colonic evaluation. Only moderate evidence exists as to whether a follow-up colonoscopy should be done in patients without high-risk lesions. An interval of five years before a control colonoscopy has been prosposed. Moderate evidence is available for surveillance with periodic colonoscopy if a high-risk lesion is found at baseline colonoscopy.

Efficacy of FOBT

The best evidence currently available concerning FOBT comes from large RCTs [12–14]. Weaker observational evidence supports the findings of these studies: three case-control studies have suggested a reduction in mortality from colorectal cancer through screening with FOBT (odds ratios of 0.4–0.9 indicated a protective effect, but bias cannot be excluded) [15–17]. In cohort studies, a population-based screening study in people aged 45–74 in France [18] reached a participation rate of 43.4% for the FOBT. The FOBT positive rate was 2.8% (2,020/71,307; non-rehydrated Hemoccult II) and 79.4% of these 2,020 patients subsequently underwent a colonoscopy.

Another ongoing study [19] screened 36034 asymptomatic individuals aged 50–80 with FOBT (Hemoccult II, with diet), followed by colonoscopy if positive, over a period of 14 years. The overall participation rate was 47.8%. During follow-up, 115 colorectal cancers were diagnosed in positive patients with 82% being early-stage and 18% being late-stage (Dukes C, D) tumours. During the same period, 312 colorectal cancers were diagnosed outside of the screening study in symptomatic patients: 57% had early-stage and 43% late-stage colorectal cancer.

Randomized Controlled Trials

The Minnesota study [13] showed a 33% reduction in mortality from colorectal cancer in the annually screened group as compared to the control group after 13 years of follow-up (but no reduction in the biennially screened group at this stage), whereas the Funen study [12] indicated that biennal screening reduced colorectal cancer mortality by 18%, independently of age and gender, although without a significant reduction in overall mortality. In the Nottingham study [14], although overall mortality was not significantly different among the tested and control groups, patients who refused the first screening test showed a higher rate of mortality. No difference in mortality could be found in the Göteborg study [20]. In all but the Göteborg study, a significant reduction in the incidence of advanced-stage cancers (C and D) was observed among the screened groups. Further details are given in Tables **2** and **3**. Table **3** includes results from the Swedish study as well as results from the French cohort study.

Table **3** shows that rehydration increases and that a special diet decreases the number of cases detected (with a reverse effect on the positive predictive value [PPV] of the test [rehydration decreases the PPV and diet increases it]).

Participation in screening programmes was generally situated between 50 and 70% [21–23]. Compliance was higher when the test was proposed by a GP (85–94.0%) than when it was sent by post (26.0–34%). Adherence to screening sigmoidoscopy after a positive FOBT ranged from 11–53% [23]. A 38% adherence rate by physicians

Table 2 Randomized controlled trials of FOBT screening vs no screening for colorectal cancer

Study	Place	N	Age	Sex (M/F)	Setting	Screening modality	Follow-up length	Diagnostic exmination in positive FOBT	Reduction mortality from colorectal cancer	Reduction in colorectal cancer incidence
Mandel [13]	Minnesota, US	46,551	50–80	22,367/ 24,184	volunteers	FOBT once a year and every two years vs no screening	13 years	colonos-copy	33 %	no
Kronborg [12]	Funen, Denmark	137,485	45–75	29,714/ 32,219	general population	biennial FOBT vs no screening	10 years	colonos-copy	18 %	no
Hardcastle [14]	Nottingham, UK	152,850	45–74	72,172/ 78,079	general population	biennial FOBT vs no screening	10 years	colonos-copy or repeated screening	15 %	no
Kewenter [20], ongoing study	Göteborg, Sweden	27,700	60–64	–	general population	FOBT twice (after 16 to 24 mo)	15 years	colonos-copy or repeated screening	–	–

to complete diagnostic evaluation in positive FOBT patients was reported [24].

Recommendations of Others

The American Gastroenterological Association (AGA) has proposed, together with other societies, guidelines for colorectal cancer screening: for people at average risk (asymptomatic, age ≥ 50 years, no other risk factors for colorectal cancer) FOBT should be proposed each year [1]. In patients tested positive, an accurate examination of the entire colon and rectum by colonoscopy is recommended. An alternative is double-contrast barium enema associated with flexible sigmoidoscopy. As the AGA recommendations did not include studies published after September 1996, the final results of the Funen and of the Nottingham study were not included. In 1996, the US Preventive Services Task Force proposed annual FOBT for all persons aged 50 and older, as one option for colorectal cancer screening [25]. In 1994, the Canadian Task Force on the periodic health examination concluded that there was not enough evidence to recommend FOBT as a screening test for colorectal cancer [26].

Follow-up Screening After a Negative Result at Complete Colorectal Evaluation

People with positive FOBT and subsequent negative colon examination, are at low short-term risk for colorectal cancer [27]. The period during which a patient will remain at low risk is uncertain; Ransohoff and Lang proposed to postpone follow-up screening for five years [11].

In a group of patients with positive FOBT who were referred for further evaluation, upper gastrointestinal lesions were identified more frequently than colonic lesions. The value of upper GI endoscopy in asymptomatic patients with positive FOBT in these circumstances is controversial [28]. Occult gastrointestinal bleeding can be detected in about half of patients with celiac sprue. Therefore, it might be worthwhile to suggest duodenal biopsies in patients with positive FOBT [29].

Negative Consequences of FOBT

The relatively low sensitivity of FOBT implies that a high proportion of colorectal cancers will be false negatives or not be detected at screening, thus giving a false sense of security to doctors and patients. In a 14-year cohort study of 27,466 patients screened, 13/21 (62 %) of patients with advanced cancers (Dukes C, D) tested negative initially [30].

The Serendipity Effect of Colonoscopy

Adenomas found through screening programmes with FOBT are likely to be detected because of the high prevalence of adenomas and the frequency of colonoscopy rather than because of the ability of FOBT to detect adenomas [26]. When discussing the Minnesota Colon Cancer Control Study, Lang and Ransohoff observed that "some of the benefit of FOBT screening may come from 'chance' selection of persons for colonoscopic examination because of the high positivity rate of FOBT that may occur for reasons other than a bleeding cancer or polyp" and concluded that up to 33–55 % of the mortality reduction could have resulted from random colonoscopy in false positive Hem-

Table 3 Results of different screening programmes using FOBT

	Nottingham 1996 [14]	Göteborg 1994 [20]	Göteborg 1997 [78]	Funen 1996 [12]	Minnesota 1993 [13]	Calvados 1996 [18]
Target population	150,251	27,700	6,367	140,000	46,551	165,000
Study period	1981–1991	1982–present	1993 and 1996	1985–1995	1975–1992	1991–1994
Setting	population-based	population-based	population-based	population-based	volunteers	population-based
Study design	RCT	RCT	RCT	RCT	RCT	Cohort
Age (yr)	45–74	60–64	55–56	45–75	50–80	45–74
Participation	59.6% (at least one screening)	66% first screening	59% (one screening)	67% (first screening)	90% (at least one screening)	43.4%
Strategy by positive FOBT	retest (FOBT) and if positive colonoscopy	digital examination, sigmoidoscopy, double contrast barium enema	flexible sigmoidoscopy and double contrast barium enema	colonoscopy	colonoscopy	colonoscopy
Colonoscopy rates by positive FOBT	NA	NA	NA	85%	nearly 80%	79%
Type of FOBT	non-rehydrated Hemoccult; with diet for retest only	with and without rehydration Hemoccult II, with diet	rehydrated; restest with dietary restriction	non-rehydrated Hemoccult II, no diet	rehydrated Hemoccult, with diet	non-rehydrated Hemoccult II, no diet
Positivity rates	2.1% (first screening) 1.2% (rescreening)	1.9% without rehydration 5.8% with rehydration	11.9% without rehydration and without diet 4.4% with rehydration and diet	1% first screening, 0.8% 2nd screening 0.9% 3rd screening, 1.3% 4th screening, 1.8% 5th screening	2.4% without rehydration 9.8% with rehydration	2.8%
Positive predictive value of FOBT for colorectal cancer	9.9% (first screening) 11.9% (rescreening)	NA	NA	17% first screening, 8% 2nd screening, 16% 3rd screening 11% 4th screening, 10% 5th screening	5.6% without rehydration 2.2% with rehydration	8.0%
Positive predictive value of FOBT for adenomas	47.1% (first screening)	32% without rehydration 22% with rehydration	NA	32% first screening, 38% 2nd screening, 27% 3rd screening, 22% 4th screening, 21% 5th screening	NA	23.5%

NA: not available

occult patients [31]. Bond responded that only 6–11% of the observed reduction in colorectal cancer mortality could be explained by this mechanism [32].

To summarize, three randomized trials from three countries demonstrated that people screened with FOBT annually or biennially, and with subsequent colonoscopy in the event of positive testing, have colorectal cancer detected at an earlier stage and have a better survival rate from colorectal cancer. No study has, however, demonstrated to date any significant reduction in the overall mortality or in the incidence of colorectal cancer in the subjects screened.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy allows a large proportion of polyps to be detected [33,34]. In several studies in asymptomatic individuals, the yield by flexible sigmoidoscopy for adenomas ranged from 6–26% and for colorectal cancer from 0.2–2% [35–40]. In two studies that examined both tests, 44–55% of adenomas detected at colonoscopy were beyond the reach of sigmoidoscopy [36,41]. In an RCT, the sensitivity of flexible sigmoidoscopy to detect an adenoma or a colorectal cancer in the rectosigmoid region has been estimated to be 87% and 85%, respectively [42]. A prospective controlled study [39] analysed the efficacy of polypectomy by flexible sigmoidoscopy screening in 400 screened and 399 control patients from the general popula-

tion (no exclusion of symptomatic patients or patients with a colorectal cancer) aged 50–59 during ten years of follow-up. In a pragmatic analysis, the population submitted to endoscopy showed significantly less cases of colorectal cancer (0/324) than the controls and non-attending individuals in the group screened (5/475).

Impact of Sigmoidoscopy Screening on Patient Outcome

Three case-control studies [43–45] suggest that sigmoidoscopy screening can reduce mortality from cancer of the distal colon and rectum. Selby [46] analysed evidence from a randomized trial of multiphase screening (Kaiser Multiphasic Evaluation Study) and stated that no conclusion could be drawn from this study as to whether screening sigmoidoscopy reduces mortality from colorectal cancer. Atkin conducted a long-term study [47] in patients who had adenomas removed by sigmoidoscopy up to 30 years previously and estimated that 80% of rectal cancers had been prevented by adenoma removal. A prospective controlled study [39] with ten years of follow-up suggested a 75% reduction in colorectal cancer incidence; the study sample was, however, too small to have sufficient power to yield a significant result.

It has been estimated that screening sigmoidoscopy should result in the detection of one or two carcinomas per 1000 patients with carcinomas being detected at an earlier stage [26].

Screening Intervals

A prospective study [48] of 217 patients with negative FOBT found a 1-year surveillance sigmoidoscopy to yield only 1% more neoplasia as compared to the baseline examination. Selby [43] showed a long duration of the protective effect of polypectomy, suggesting an interval as great as ten years. This interval is also suggested by a controlled follow-up study in Norway [39].

A recent case-control study [45] found that polypectomy retained its efficacy over five to six years. Rex et al. [49] found an adenoma prevalence of 6% but no colorectal cancer after two years in asymptomatic average-risk men aged ≥ 50 years with a high socio-economic status. He suggested a screening interval of five years after a negative examination.

Compliance

A survey [50] explored obstacles to compliance with screening sigmoidoscopy and found fear of pain to be the main barrier to compliance, and that clinician advice, a family member with a history of screening sigmoidoscopy and the perceived benefit of the test were associated with a higher degree of utilisation. Although low compliance (12–27%) has been found in community-based interventions [38, 51], much higher acceptance rates (87–95%) have been observed in particular settings (City of Boston employees, US State Department personnel) [37, 52].

Recommendations of Other Authors

According to the AGA recommendation, a screening sigmoidoscopy every five years should be proposed [1]. Polyps < 1 cm should be biopsied, and if adenomatous polyps or cancer are found, the patients should be offered colonoscopy as well; if large (> 1 cm) polyps are found, colonoscopy should be recommended. The Canadian Task Force on the periodic Health Examination considered, in 1994, that the evidence was insufficient to recommend screening with flexible sigmoidoscopy in people > 40 years (grade C recommendation) [26]. The US Preventive Services Task Force proposed sigmoidoscopy, without any interval being specified, as one option for colorectal cancer screening [25].

An alternative prosposal is to perform a single screening sigmoidoscopy at age 55. This rationale stems from the observation that the prevalence of distal adenomas increases rapidly after the age of 50 and stabilizes at age 60. Moreover, adenoma in the distal colon are considered to be indicators of lesions in the proximal colon [53]. A multicentre randomized trial [54] to evaluate "once-only" flexible sigmoidoscopy is currently in progress in the UK. With attendance rates of up to 74%, preliminary results show a detection rate of 0.007 for colorectal cancer (higher that expected) and of 0.1 for adenomas.

Combined Fecal Occult Blood Test and Flexible Sigmoidoscopy

Screening including both tests has been recommended by the AGA group [1] and by the WHO Collaborating Center for the Prevention of Colorectal cancer [55]. FOBT once a year and sigmoidoscopy every three years [55] or five years [1] have been prosposed. Using indirect evidence from a mathematical model, Eddy [56] suggested that screening patients aged 50–75 years using FOBT plus flexible sigmoidoscopy every three to five years should reduce the risk of dying from colorectal cancer by 10–75% depending on the screening option.

Double-Contrast Barium Enema

Reports of RCT's of screening for colorectal cancer with double-contrast barium enema (DCBE) have not been found. One strategy proposed consists of offering double-contrast barium enema every five to ten years [1]. This method is considered safer than colonoscopy or sigmoidoscopy but small polyps may go undetected. For colorectal cancers and large polyps (≥ 1 cm), the accuracy of double-contrast barium enema has been considered almost as good as that for colonoscopy [1]. However, in a retrospective study assessing the relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer, colonoscopy was found to be more sensitive (97% vs. 87%) [57].

Another study [58] found a sensitivity of DCBE of 80% and 77% for colorectal cancer and adenomas, respectively.

Double-contrast barium enema is considered a good technique for colorectal cancer surveillance in Hereditary Non-Polyposis Colorectal Cancer, ulcerative colitis and flat adenoma syndrome (i.e. in situations in which small details of the mucosa should be analysed) [59].

Combining double-contrast barium enema and flexible sigmoidoscopy in patients with a positive FOBT provides sensitivities for detecting a colorectal cancer ranging from 90–98% and from 96–99% for adenomas ≥ 1 cm [42, 58].

Perforation and mortality rates of 1 : 10 000 and 1 : 50 000, respectively, have been reported for flexible sigmoidoscopy [60].

Colonoscopy

Apparently, no controlled study has evaluated whether colonoscopy alone reduces the incidence or mortality from colorectal cancer in people at average risk of the disease [1]. To perform a screening colonoscopy every 10 years has been proposed [1]. Uncontrolled prospective studies of screening colonoscopy in average-risk asymptomatic persons have been examined by Rex in a non-systematic review [61]. The yield of adenomas diagnosed ranged from 13–41%; the figure was 0–2.2% for colorectal cancer [36, 41, 62–64]. Similar data were observed in another study [40]. However, most data come from diagnostic evaluations and surveillance, and not from screening studies. Small polyps (< 5 mm) could be missed in 25% of cases and polyps > 1 cm in up to 10% of cases [1, 65]. In two prospective studies of screening colonoscopy, the caecum was reached in over 98% of cases [63, 66].

Impact of Screening Colonoscopy on Patient Outcome

Despite the high yields from screening colonoscopy for adenomas and colorectal cancer, the absence of a control group or of follow-up does not permit analysis of the effectiveness of screening by colonoscopy [26]. Some authors advocate screening colonoscopy in average-risk males ≥ 60 years old, taking into account the higher prevalence of adenomas in this subgroup [61]. Indirect evidence from a case-control study [45] supports the efficacy of colonoscopy in reducing the risk of colorectal cancer. The AGA recommendations indicate that a colonoscopy every ten years is an option in average-risk individuals [1].

The use and benefit of colonoscopic polypectomy is described in detail in the joint article on colorectal polyps [67].

People at Increased Risk of Colorectal Cancer

The use of colonoscopy for surveillance in patients with inflammatory bowel disease is examined in another article published in the same issue of the Journal [68].

People with Close Relatives who Have Had Colorectal Cancer or an Adenomatous Polyp

In seven prospective trials examining the yield from screening colonoscopy in persons with a positive family history of colorectal cancer, adenomas were found in 18–36% and colorectal cancer in 0–2% of the patients [61]. In a prospective controlled trial [69] from the Telemark Polyp Study, 53% of adenomas were found in relatives vs. 33% in the general population (historical controls), and 1.7% of colorectal cancer vs. 0.3% respectively. Thirty-five percent of polyps were located proximally.

A non-randomized controlled trial [64] compared screening colonoscopy in asymptomatic first-degree relatives of colorectal cancer patients with asymptomatic controls without a personal or a family history of colorectal cancer: 14.4% of study patients had adenomas vs. 8.4% of controls, and 48% and 25% respectively were beyond the reach of flexible sigmoidoscopy. Age, gender and a history of colorectal cancer in first-degree relatives were independently associated with the presence of adenomas. However, another controlled trial [70] found no relationship between a family history of a single first-degree relative and a higher prevalence of colorectal cancer or adenomas, except if the cancer in the relative was diagnosed before the age of 60. According to Rex, the yield of colonoscopy to detect colorectal neoplasia in patients with a positive family history has been surprisingly "low" so far [61]. Indeed, we could find no study showing decreased overall mortality from colorectal cancer in first-degree relatives undergoing a screening programme.

A non-systematic review [71] found compliance rates for screening colonoscopy between 42% and 69%, in first-degree relatives of persons with colorectal cancer. Compliance was lower (30%) in an Italian pilot cohort study of 802 first-degree relatives of colorectal cancer patients [72], but higher (82%) in an Norwegian study [69].

Recommendations of Others

According to the AGA, first-degree relatives of individuals with colon cancer should be offered the same options as average-risk people but beginning at age 40 years. If the close relative was diagnosed with colorectal cancer before the age of 55 years or with an adenomatous polyp before age 60, special efforts should be made to ensure that screening takes place [1]. Similar proposals have been made by the WHO Collaborating Center for the Prevention of Colorectal Cancer [55].

People with a Family History of Familial Adenomatous Polyposis (FAP)

These patients should receive genetic counseling and consider undergoing genetic testing to see if they are gene carriers. A negative genetic test result rules out FAP only if an affected family member has an identifiable mutation. Gene carriers or indeterminate cases should be offered flexible sigmoidoscopy every twelve months beginning at puberty to see if they are carrying the gene. If polyposis is present, they should begin to consider at what stage they should have a colectomy. FAP has an autosomal dominant inheritance and people with FAP have a 100% chance of developing colorectal cancer [1].

People with a Family History of Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

HNPCC is the most common hereditary form of colorectal cancer (nearly 10% of all colorectal cancer cases). An accelerated adenoma-carcinoma progression has been suggested because of the presence of larger adenomas with more dysplasia than in non-familial cases [73]. Two-thirds of cancers occur in the right colon (nearly 70% proximal to the splenic flexure) and a majority of synchronous and metachronous cancers have been observed [73]. An examination of the entire colon is thus necessary.

We only found one prospective controlled study [74] of screening for colorectal cancer in HNPCC families. Most of the available evidence is otherwise observational. Järvinen [74] and colleagues found that a 3-year interval colonoscopy (or double-contrast barium enema and flexible sigmoidoscopy) screening in families with HNPCC reduces the colorectal cancer rate of 62% within a 10-year follow-up period. In the screening group, six colorectal cancers were identified (6/133) and in the control group 14 (14/118). A probable reduction in the colorectal cancer death rate should be achieved, but the reduction in this study did not reach statistical significance.

No consensus exists with regard to the interval betwen consecutive examinations [75]. Lynch et al. recommend initiating colonoscopy at age 20–25 years with intervals of one to two years [73].

Recommendations of Other Authors

People with a family history of colorectal cancer in multiple close relatives and across generations, especially if cancers occur at a young age, should receive genetic counselling and consider undergoing genetic testing for hereditary non-polyposis colorectal cancer. They should be offered an examination of the entire colon every one to two years starting between the ages of 20 and 30 years, and every year after age 40 [1]. An US task force (Cancer Genetics Studies Consortium [CGSC]) [76] recommends a full colonoscopy every one to three years beginning at age 20 to 25 years, for individuals known to be carriers of HNPCC-associated mutations (and for those with a substantial likelihood of being mutation carriers).

2. Panel Results

Considering the above review of relevant literature, the panel evaluated 37 specific theoretical patient scenarios related to screening for colorectal cancer in asymptomatic patients without a personal history of colorectal cancer or polyps, using an explicit two round modified Delphi panel expert method (RAND appropriateness method) which is described in a joint publication [5].

Definition of Terms Used

The terms and definitions were reviewed and approved by the panelists, they are listed in Table **4**.

Table 4 Definition of terms

Risk for colorectal cancer	
Slight risk	
Any of the following:	– colorectal cancer in one first degree relative – colorectal cancer in two second degree relatives – adenomatous polyp in one first degree relative – personal history of breast, ovarian or endometrium cancer – history of breast, ovarian and endometrium cancer in one first degree relative
Moderate risk	
Any of the following:	– colorectal cancer in two first degree relatives – colorectal cancer in one first degree relative with onset before 50 years of age
High risk	
Any of the following:	– family history of familial adenomatous polyposis (FAP) – family history of non-polyposis hereditary colorectal cancer (NPHCC)
First degree relatives: parent, children, siblings	
FOBT positive stool	
At least one stool test for occult blood shows a positive reaction	
Lower GI evaluation	
Sigmoidoscopy: flexible tube (60 cm) Barium enema: double contrast technique	

Clinical Variables Used

The clinical variables used to create and rate detailed patient scenarios to evaluate the appropriateness of use of colonoscopy for screening for colorectal cancer in asymptomatic individuals and for screening for colorectal cancer in asymptomatic individuals with a positive FOBT screening are shown in Table **5**.

Table 5 Clinical variables used to assess appropriateness of use of colonoscopy in asymptomatic individuals without personal history of colorectal cancer or polyps (18 items), and in asymptomatic individuals with a positive screening FOBT without a personal history of colorectal cancer or polyps (3 items)*

Variables	Number of categories	Categories
Age	6	if no increased risk < 50 years ≥ 50 years if slight to moderate risk < 40 years ≥ 40 years if high risk < 20 years ≥ 20 years
Risk factor(s) for colorectal cancer	5	no increased risk slight risk moderate risk high risk – NPHCC high risk – FAP
Interval since last colonoscopy	4	no prior colonoscopy < 5 years ago 5 – < 10 years ago ≥ 10 years ago
Evaluation done	3	– no barium enema or sigmoidoscopy performed – barium enema with sigmoidoscopy revealed no bleeding source – barium enema or sigmoidoscopy revealed potential bleeding source

General Panel Results for Screening for Colorectal Cancer in Asymptomatic Patients

Colorectal cancer screening in asymptomatic patients was assessed in 34 clinical scenarios for five categories of risk of developing colorectal cancer, according to age and interval since a previous colonoscopy. Three additional scenarios referred to positive FOBT screening in asymptomatic patients. Of the 37 scenarios, the panel rated 22% (8) as inappropriate, 32% (12) as uncertain and 46% (17) as appropriate. The rate of overall agreement was high (72% of the scenarios).

Specific Clinical Panel Results for Screening for Colorectal Cancer in Asymptomatic Patients

The main results are worded as overall statements representing several clinical scenarios. In some cases, the same scenario may apply to more than one statement. Over 90% (34/37) indications could be characterized by the six overall statements given in Table **6**. Detailed appropriateness and necessity criteria, including voting distribution for all 37 theoretical scenarios, are available in a computerized form accessible via Internet at the EPAGE web site (http://www.epage.ch).

Table 6 Description of appropriateness of indications for colonoscopy for screening for colorectal cancer in asymptomatic individuals

Clinical situation
In individuals with average risk for colorectal cancer, indication for colonoscopy is *inappropriate* under 50 years of age; *uncertain* in individuals aged 50 and over
In individuals with a slightly increased risk for colorectal cancer, colonoscopy is *inappropriate* under 40 years of age; *uncertain* in patients aged 40 and over unless a colonoscopy has been performed less than 5 years previously (inappropriate) or more than 10 years previously (appropriate)
In individuals with a moderately increased risk for colorectal cancer, indication for colonoscopy is *uncertain* under 40 years of age, unless a colonoscopy has been performed less than 5 years previously (inappropriate); *appropriate* in patients aged 40 and over
In patients at high risk due to NPHCC, indication for colonoscopy is *uncertain* in most scenarios
In patients at high risk due to FAP, indication for colonoscopy is *appropriate* in most scenarios
In presence of a positive screening FOBT, indication for colonoscopy is *appropriate*

Description of Necessity

Ten out of 37 scenarios (27%) were judged necessary. All necessary indications for screening for colorectal cancer in asymptomatic patients were related to patients at moderate or high risk to develop colorectal cancer (Table **7**).

Table 7 Description of necessity of indications for colonoscopy for screening for colorectal cancer in asymptomatic individuals

Clinical situation
In individuals with a moderately increased risk for colorectal cancer, indication for colonoscopy is *necessary* in patients aged 40 or more unless a colonoscopy has been performed less than 10 years previously
In patients at high risk due to HNPCC, indication for colonoscopy is *necessary* in patients aged 20 or more who had a previous colonoscopy at least 10 years previously
In patients at high risk due to FAP, indication for colonoscopy is *necessary* in most scenarios

Conclusions

The AGA guideline, published in 1997, considers that there is strong evidence to support screening for colorectal cancer. "Evidence exists that reductions in colorectal cancer mortality can be achieved through detection and treatment of early-stage colorectal cancers and the identification and removal of adenomatous polyps, the precursor of these cancers" [1]. According to these recommendations,

several tests offer a sufficiently high level of performance and effectiveness, so that one should take into account the patient's preferences, the patient's age and comorbidity as well as local resources and expertise availability [1].

However, these recommendations have been considered too optimistic, given for instance that the Nottingham [14] and the Funen studies [12], conducted among the general population (as opposed to the all-volunteer Minnesota study [13]) indicated a reduction of 15–18% in mortality due to colorectal cancer, a result that may well be much lower when screening is applied in daily practice [77].

To perform a colonoscopy every ten years has been proposed as an effective option for colorectal screening. This is a very expensive option and there is no solid data to support this proposal to date.

Using colonoscopy as a screening tool for colorectal cancer in asymptomatic individuals at no increased risk was judged inappropriate in patients aged under 50 by the EPAGE panel, whereas the indication was rated uncertain in individuals aged 50 or more. When a screening FOBT was positive, colonoscopy was considered appropriate but not necessary.

Colonoscopy was more often judged appropriate in patients with at least moderate risk for developing colorectal cancer. However, the EPAGE panel was uncertain about the appropriateness of use of colonoscopy to screen for colorectal cancer in patients at increased risk because of HNPCC. Given the relative disagreement of the EPAGE panel with the (limited) published evidence, the panelists will be formally asked to reexamine their position during the Summer of 1999. In patients with FAP, colonoscopy was considered appropriate and necessary in almost every clinical scenario proposed. Full panel results can be consulted at the EPAGE web site (http://www.epage.ch).

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