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Colorectal Cancer Prevention 2000: Screening Recommendations of the American College of Gastroenterology

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer death in the United States (1). Physicians and lay persons are becoming increasingly aware that most colorectal cancers and most deaths from colorectal cancer are preventable through screening. Screening is the search for cancer and precancerous polyps (adenomas) in asymptomatic persons. Colorectal cancer has several features that make it ideal for screening. First, it is both common and serious (fatal if not identified early or left untreated). Second, it has a readily identifiable and slow growing precursor lesion, the adenoma, removal of which prevents progression to cancer (2, 3, 4). Third, colorectal cancer, once developed, is believed to advance relatively slowly from stages that are readily curable by surgery (Dukes A and B) to stages that are not (Dukes C and D). Fourth, currently recommended prevention tests are widely available.

The American College of Gastroenterology (ACG) is an organization of over 7,300 gastroenterologists and other health care professionals with special interest in GI medicine. The interests of the ACG are education and research in clinical gastroenterology and

supporting clinical gastroenterologists in the care of their patients. The ACG has previously endorsed the 1997 colorectal cancer screening guideline of the Agency for Healthcare Policy and Research (AHCPR) (5). The AHCPR's recommendations presented a menu of options (Table 1) for screening average-risk persons. These options have similar cost-effectiveness ratios (5, 6). However, there are substantial differences between the various options regarding their effectiveness, initial costs, and to a lesser degree, risk. The ACG continues to endorse the AHCPR guideline.

Table 1. Options for Average-Risk Screening Beginning at Age 50 in the AHCPR Guideline

- Annual FOBT
- Flexible sigmoidoscopy every 5 yr
- Annual FOBT plus flexible sigmoidoscopy every 5 yr
- Double-contrast barium enema every 5-10 yr
- Colonoscopy every 10 yr

AHCPR = Agency for Healthcare Policy and Research; FOBT = fecal occult blood testing.

This paper outlines the preferred colorectal cancer screening recommendations of the ACG and represents an update of the ACG position on screening represented in the AHCPR guideline. The ACG undertook the development of updated screening recommendations for the following reasons. First, continual expansion in the use of lower bowel endoscopy, and improved understanding of the effectiveness of colonoscopy and polypectomy, combined with decline in the use of barium enema, have established clinical gastroenterologists at the forefront of colorectal cancer prevention. This updated recommendation is meant to reflect trends in the rapidly changing perceptions of colorectal cancer prevention strategies among clinical gastroenterologists in both academic and private practice. Second, scientific publications concerning colorectal cancer screening appear regularly. Therefore, regular updates in colorectal cancer screening recommendations are needed to reflect new data.

These recommendations were developed by a panel of ACG members with expertise in colorectal cancer screening. The panel was appointed by the executive committee of the ACG, and these recommendations were reviewed and approved by the Board of Trustees and the Publications Committee of the ACG.

AVERAGE-RISK SCREENING

Definition: Persons age 50 and older are at average risk if they have no risk factors for colorectal cancer other than age.

Preferred Screening Strategy: Colonoscopy Every 10 yr

Colonoscopy has not been studied in randomized controlled trials or case control studies to demonstrate its effectiveness as a screening test on colorectal cancer mortality. Only cross-sectional studies using colonoscopy in asymptomatic average-risk persons have been performed thus far (7, 8, 9, 10, 11, 12, 13, 14, 15). However, several lines of evidence suggest colonoscopy is the most effective colorectal cancer prevention test currently available. First, case control studies of sigmoidoscopy have demonstrated a 60-70% reduction in colorectal cancer mortality in the distal colon from sigmoidoscopy and polypectomy (16, 17). These studies were performed largely with rigid protosigmoidoscopes and have been widely extrapolated to establish the effectiveness of flexible sigmoidoscopy. However, the studies indicate the effectiveness of endoscopy and polypectomy and can be extrapolated to establish the effectiveness of colonoscopy and polypectomy. Second, a cohort of patients who underwent colonoscopy and clearing of colon adenomas by polypectomy experienced a 76-90% reduction in colorectal cancer incidence

compared to reference populations, and there were no deaths from colorectal cancer (2). This dramatic reduction in incidence and mortality of colorectal cancer occurred in a population of patients with adenomatous polyps that is at much higher risk for colorectal cancer than is a screening population. This finding underscores the remarkable potential effectiveness of colonoscopy and polypectomy as a colorectal cancer prevention strategy. Further, it establishes that effective identification and removal of adenomas is the central element of colorectal cancer incidence and mortality reduction. Third, cross-sectional studies of screening colonoscopy (7, 8, 9, 10, 11, 12, 13, 14, 15) in average-risk persons consistently demonstrate a prevalence of adenomas more than twice that detected on average by flexible sigmoidoscopy (18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33). Colonoscopy is also substantially superior to barium enema for adenoma detection. In the only study of barium enema as a screening test, single-contrast barium enema (SCBE) led to detection of adenomas in only 2% of the screenees (34). Double-contrast barium enema (DCBE) has not been used in a screening study. However, in a surveillance population with a spectrum and prevalence of disease comparable to a screening population, using a study design which optimized DCBE sensitivity, DCBE detected only 50% of adenomas > 1 cm in size (35). Thus, colonoscopy is currently the dominant strategy available for adenoma detection. Fourth, retrospective (36, 37, 38, 39, 40, 41, 42) and prospective (43) studies of colonoscopy findings in patients with colon cancer proximal to the splenic flexure have consistently found that at least two-thirds of these patients have no neoplasm distal to the splenic flexure. Currently nearly 40% of colorectal cancers in the United States arise proximal to the splenic flexure (44). Thus, flexible sigmoidoscopy will be normal in a substantial proportion of patients with colorectal cancer. Fifth, screening colonoscopy is an appropriate adjustment to the progressive shift of colorectal cancer toward the proximal colon in the United States. Although most cancers still occur in the distal colon, several studies have suggested a proximal shift over the past 30 yr (45, 46, 47). This may reflect an aging population in which older patients are more likely to develop right-sided cancers. Many patients with serious proximal neoplasia would go undetected with only a distal colon examination.

Colonoscopy every 10 yr has several additional advantages over other screening strategies. It allows long interval protection (Table 1), providing an opportunity for improved compliance. It allows diagnosis and treatment in a single session, decreasing the risk of patients being lost to follow-up after detection of polyps by tests with only diagnostic capability. Single-session diagnosis and treatment also

increases convenience for patients, and reduces indirect costs associated with lost work time. The use of sedation for most colonoscopies in the United States leads to reduction in pain and improved patient satisfaction (48). These outcomes are important aspects of improving public perception of colorectal cancer prevention tests and improving compliance (49, 50, 51, 52).

The interval at which screening colonoscopy should be performed in average-risk persons has not been determined by observational studies. The longest reported interval at which a group of asymptomatic average-risk persons age 50 with an initial normal colonoscopy has undergone a second colonoscopy is 5.5 yr (53). The incidence of cancer was 0% at 5.5 yr, and the incidence of adenomas with advanced pathology was <1%. In a case-control study, sigmoidoscopy appeared to prevent deaths from rectal cancer for 10 yr (16). Some experts have suggested that average-risk persons could be triaged into high- and low-risk groups by once-in-a-lifetime sigmoidoscopy (54) or colonoscopy (7, 10). Colonoscopy at 10-yr intervals will not prevent all colorectal cancers or colorectal cancer deaths (55, 56, 57, 58, 59). However, given the above data as well as information on the growth rate of adenomas (60) and the time sequence of the adenoma-carcinoma sequence (61), screening colonoscopy at 10-yr intervals seems reasonable pending the availability of observational studies. Simple innovations such as the transparent cap may make the sensitivity of colonoscopy higher and 10-yr intervals even safer (62, 63).

Colonoscopy has been found to be cost-effective both in comparison to other colorectal cancer screening strategies and to other accepted healthcare practices. Lieberman compared the cost-effectiveness of the five strategies listed in the AHCPR average-risk menu (64). The model included the costs of initial screening, evaluation of positive tests, and the costs of care for cancers that were not prevented. Fecal occult blood testing (FOBT) alone was the most cost-effective strategy, but colonoscopy every 10 yr became the most cost-effective strategy if the charge for diagnostic colonoscopy was under \$750. Provenzale et al. examined the cost-effectiveness of five strategies for average-risk individuals age 50 and older in a managed care plan (65). These strategies were 1) colonoscopy every 10 yr; 2) barium enema every 5 yr; 3) annual FOBT plus flexible sigmoidoscopy every 5 yr for annual FOBT; and 5) no screening. The authors took the perspective of the health maintenance organization and used the actual variable costs for procedures and treatments at Duke University including radiation, chemotherapy, postoperative, and hospice care. The cost for diagnostic colonoscopy was \$650. Screening colonoscopy was the most effective strategy and was

cost-effective compared to other common practices. The incremental cost-effectiveness ratio for screening colonoscopy was \$6,600/life year (LY) gained, compared to \$22,000/LY gained for breast cancer screening, \$160,000/LY gained for heart transplantation and \$250,000/LY gained for cervical cancer screening. The progressive decline in colonoscopy reimbursement has resulted in colonoscopy prices that presently are often sufficiently low enough to make colonoscopy the most cost-effective colorectal cancer screening strategy, and consistently low enough that screening colonoscopy is cost-effective compared to other accepted screening practices and health care practices. Further, colonoscopy reimbursement is projected (using Medicare data) to fall further. Thus, although effectiveness is the primary rationale for recommendation of screening colonoscopy as the ACG preferred screening strategy in average-risk persons, the strategy of colonoscopy every 10 yr is also cost-effective compared to other well-accepted practices.

The risks of colonoscopy include diagnostic and therapeutic perforation and bleeding related to polypectomy. Complications related to removal of large polyps are unavoidable at the present time, as other screening strategies that identify these polyps will also result in colonoscopy and polypectomy. The use of colonoscopy for screening does result in removal of a number of small polyps, many of which would never result in cancer. Polypectomy in these cases occasionally results in bleeding, but perforation is rare. The current rate of perforation from diagnostic colonoscopy is uncertain, but may be on the order of one in several thousand colonoscopies (66, 67, 68, 69). Thus, the risk of perforation from instrument passage appears to have decreased with time (70, 71, 72). The risk of perforation in asymptomatic persons is likely reduced. For example, in the first studies of screening colonoscopy reported (7, 8, 9, 10, 11, 12, 13, 14, 15), not a single perforation has occurred in more than 5,000 screenees.

The ACG recognizes that reimbursement for screening colonoscopy is generally unavailable at this time. However, the arguments in favor of screening colonoscopy are compelling from the perspectives of both effectiveness and cost-effectiveness. This strategy has such enormous potential to impact colorectal cancer incidence and mortality, that it is designated the preferred strategy whenever resources and appropriately trained experts are adequate to supply it and reimbursement is available. We anticipate a progressive shift over the next several years from the alternative strategy (below) to the preferred strategy of screening colonoscopy. Although the ACG recommends colonoscopy every 10 yr beginning at age 50, we recommend additional

study to determine the optimal time to begin colonoscopy. For example, where resources are limited, the strategy of flexible sigmoidoscopy plus FOBT at age 50 yr followed by colonoscopy at age 60 yr also deserves consideration. Such a strategy acknowledges the substantial increase in the prevalence of asymptomatic cancers and advanced adenomas between age 50 and 60 yr (73), and the progressive shift of colorectal cancer toward the proximal colon with advancing age (45, 46, 47). Similarly, an argument can be made to initiate screening in average-risk subjects at age 55-60 yr based on age-related prevalence rates of colorectal cancer and advanced adenomas (73). As a corollary of this, a single colonoscopy at age 60 yr may be sufficient for life if it identifies most high-risk individuals (7, 10). Additional study is needed of the risk of serious neoplasia if a colonoscopy at age 55-60 yr is negative for neoplasia.

The recommendation of screening colonoscopy has important implications for postpolypectomy surveillance colonoscopy. Cost-effectiveness analyses of screening colonoscopy are very sensitive to the interval of postpolypectomy surveillance colonoscopy (64, 74). Recent data suggest that average-risk persons with one or two tubular adenomas can have their initial follow-up colonoscopy at 5 yr, and most other patients with adenomas can be examined at 3 yr (5, 75). Adherence to recommended intervals in patients with complete removal of neoplasia will improve the cost-effectiveness of screening colonoscopy and help to make available the necessary resources to perform screening colonoscopy.

Alternative Strategy: Flexible Sigmoidoscopy Every 5 yr Plus Annual FOBT

This screening strategy is recommended when resources, expertise, or reimbursement for screening colonoscopy are not available. Sigmoidoscopy and polypectomy have been shown to reduce mortality from rectal cancer in two well-designed case-control studies (16, 17). These studies, performed largely with rigid proctosigmoidoscopy, have been widely extrapolated as the basis for the effectiveness of flexible sigmoidoscopy. Sigmoidoscopy has several advantages: 1) it is inexpensive; 2) it is usually performed with less bowel preparation than colonoscopy; 3) it does not generally employ sedation; and 4) it is often performed by primary care physicians. Several of these features can also be considered disadvantages. For example, preparation is often a limiting factor in instrument advancement and visualization, as are pain, looping, and previous abdominal surgery in women (76, 77). Lack of sedation results in reduced satisfaction in many patients, and may lead to unwillingness to return to follow-up examinations or contribute to an overall

negative public perception of colorectal cancer prevention tests. Primary care physicians have been shown to be more likely than gastroenterologists to miss significant neoplasms while performing lower bowel endoscopy (44). Finally, sigmoidoscopy is more often performed in office settings than is colonoscopy. Whether primary care office practices maintain the standards for endoscopic procedures that are observed in hospitals and ambulatory surgery centers has been a matter of concern (78).

The optimal interval for screening flexible sigmoidoscopy remains uncertain. Several studies have examined the incidence of adenomas detected at a second examination after an initial negative sigmoidoscopy (79, 80, 81, 82). The interval between examinations in these studies has been short (1, 1, 1 in 3 yr). The incidence of adenomas and adenomas with advanced pathology has been uniformly low. Therefore, intervals of 5 yr as currently recommended in the AHCPR guideline should be adequate. The protective effect of sigmoidoscopy for 10 yr cited above (16) suggests that longer intervals would be adequate. A study of once-in-a-lifetime sigmoidoscopy is in progress in England (83). Given that sigmoidoscopy is often limited in extent, can be impaired by preparation, and has lower costs than colonoscopy, the ACG recommends that it be performed at 5-yr intervals but anticipates eventual expansion of these intervals.

FOBT is the only colorectal cancer prevention test that has been examined in randomized controlled trials (67, 84, 85). FOBT followed by colonoscopy for all positive tests has been associated with a 33% reduction of mortality from colorectal cancer when performed annually with rehydration (67) and with a 15-18% reduction when performed biannually without rehydration (84, 85). The American College of Physicians recommended that rehydration not be used (86). However, arguments have been made that a portion of the benefit results from the very high percentage of screenees [38% in the University of Minnesota Trial (67)] who receive colonoscopy when rehydration is used (87, 88). The limitations of FOBT are so substantial that the American Cancer Society declined to recommend it as a single test (89), and some experts have argued for abandoning FOBT entirely (90). Sensitivity for detection of cancer is only 33-50% for one-time testing (67, 91), but it improves if testing is repeated every 1-2 yr, requiring strict compliance. Moreover, FOBT alone is not particularly effective for cancer prevention because most patients with adenomas will have negative tests (7, 10). The ACG endorses annual FOBT and recommends that rehydration be at the discretion of the professional performing the test. Based on recent data (92), the ACG considers testing stool obtained by digital rectal examination to be appropriate as there is no increase in

false-positives. However, the sensitivity of this practice remains unknown and, thus, persons with negative tests by digital rectal examination should still undergo standard home FOBT.

Patients with positive FOBT should undergo colonoscopy (67, 84, 85). Use of double-contrast barium enema to evaluate a positive FOBT has consistently been associated with miss rates for cancer of 25% (93, 94, 95, 96, 97). Failure of primary care physicians to evaluate positive FOBT is a major concern in clinical practice (98, 99, 100, 101, 102, 103). Patients with adenomas detected at sigmoidoscopy should undergo colonoscopy (104, 105, 106), although the predictive value of small tubular adenomas in the distal colon for adenomas with advanced pathology in the proximal colon has been questioned (107, 108, 109). Prospective studies employing initial sigmoidoscopy followed by colonoscopy of all screened persons (110) will be needed to settle the current controversy. Pending final results of such studies, the ACG continues to recommend colonoscopy for all persons with adenomas at flexible sigmoidoscopy (111).

Patients undergoing FOBT and flexible sigmoidoscopy should be aware of the limitations of each test. They should understand that development of colorectal symptoms after one or both of these tests are negative should lead to re-evaluation by colonoscopy.

OTHER SCREENING STRATEGIES

Barium Enema

SCBE is generally considered inferior to DCBE for detection of colorectal polyps (112), which is a major goal of screening. In the only cross-sectional study using SCBE for screening, SCBE led to the detection of adenomas in only 2% of screenees (34). In another report, a series of patients presented with cancer shortly after one or more negative SCBE examinations (113). A number of these cancers were fatal. Thus, SCBE is not recommended for colorectal cancer screening.

DCBE is the least expensive screening test that examines the entire colon. However, DCBE has not been evaluated as a screening test in randomized trials, case-control studies, or cross-sectional studies. DCBE is inferior to colonoscopy for detection of colorectal cancer (44) and polyps (114), and has been deemed so by an independent panel (6). As noted previously, DCBE detected only 50% of adenomas >1 cm in size in the National Polyp Study (35). Although the cohort examined in the National Polyp Study was a surveillance population, it was very similar to a screening population with regard to spectrum and prevalence of colorectal neoplasia. DCBE has in the past generally been combined with flexible sigmoidoscopy (115, 116, 117). The recommendation in recent guidelines (5, 89) to use DCBE as a single

test is not well founded. In a recent trial, DCBE missed 26% of rectosigmoid adenomas >1 cm and 25% of rectosigmoid cancers in patients with positive fecal occult blood tests (93). In another recent study, DCBE missed 87% of rectosigmoid polyps 0-9 mm in size in the rectosigmoid and 67% of rectosigmoid polyps >9 mm in size (118). These studies highlight the major deficiencies in polyp sensitivity of DCBE in appropriately blinded studies.

Because of the absence of data on DCBE in screening populations, combined with significant deficits in sensitivity as noted above, the ACG does not recommend DCBE as the primary screening strategy in average-risk persons. However, in selected situations where individual radiologists take a strong interest in DCBE and have established a pattern of high-quality DCBE as estimated by local clinicians, the ACG considers that DCBE is an acceptable substitute for flexible sigmoidoscopy in the alternative primary strategy. Because of its poor sensitivity, DCBE should be performed in conjunction with annual FOBT, and positive FOBT should result in colonoscopy. Alternating sigmoidoscopy with DCBE, so that one examination is performed at 5 yr and the other at 10 yr, may also have merit.

If DCBE is used as a substitute for flexible sigmoidoscopy in the alternative primary screening strategy, it should be performed at 5-yr intervals. Low sensitivity would seem to make intervals longer than 5 yr unwise. Poor specificity (85-90%) for polyps is problematic if the test is performed more frequently.

CT and MR Colonography (Virtual Colonoscopy)

Technical performances of CT and MR colonography (virtual colonoscopy) have been evolving rapidly. At this writing, one group has reported high sensitivity and specificity for polyps as small as 6 mm in size using CT colonography (119). However, others have reported inadequate sensitivity and/or specificity for polyps on the 6-9 mm range (120) and larger polyps (121). Very little data are available in screening populations. CT colonography is less cost-effective than colonoscopy (122), and MR colonography is much less cost-effective than colonoscopy.

At this time, CT and MR colonography are not recommended for colorectal screening. Additional data on sensitivity and specificity are needed. Acceptability has been suggested to be a potential major advantage (119), but additional data are needed (123). There is no information on the appropriate interval at which CT or MR colonography should be performed. The ACG anticipates that recommendations regarding CT and MR colonography will be regularly re-evaluated as additional studies are reported.

HIGH-RISK SCREENING

High-risk colon cancer screening refers to screening for and within families with the rare syndromes of familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), and screening persons with positive family histories that do not meet clinical criteria of the well-defined syndromes. The syndromes are important because of the extreme risk of colon cancer, but together account for only 1-2% of colon cancer cases in the U.S. Cancer risk in the less well-defined category of positive family history is not nearly as high as in the syndromes. The importance of this group, however, derives from its frequency. Approximately 10% of persons in the U.S. will eventually have an immediate relative with colon cancer. This family history approximately doubles one's risk for this malignancy. Other high-risk groups for colorectal cancer, including those with a personal history of colorectal cancer or adenomas and those with ulcerative colitis or Crohn's colitis, are generally considered to undergo surveillance rather than screening, and are not addressed in the present recommendations.

FAP

Children of persons with known FAP should have sigmoidoscopy screening every 1-2 yr, beginning at 10-12 yr of age. Once polyps emerge, an appropriately timed colectomy can be planned. Older, unscreened, relatives of a person newly diagnosed with FAP should have full colonoscopy for the first screening examination in view of the risk of more fully developed polyposis. Screening should continue until age 40, and then be replaced with standard-risk screening.

Genetic testing is now available for the diagnosis of FAP within families clinically known to have the condition. It can be used to determine which family members actually need endoscopic screening. The genetic test is based on finding the disease-causing mutation (or indirect evidence of a mutation) in the adenomatous polyposis coli (APC) gene. Present techniques allow successful identification of an APC mutation in almost 80% of FAP families (124). The best use of genetic testing is to first test a family member clinically known to have FAP. Testing will be successful in almost 80% of such cases. Once a mutation is found in the index case, other family members can be tested with near 100% accuracy, as all affected family members would have the same mutation. Screening in the family can then be based on which persons carry the mutant gene. If a mutation is not found in the index case, however, genetic testing must be considered unsuccessful in that family and all persons at risk need to undergo endoscopic screening. Genetic counseling is an important adjunct to genetic testing so both the physician and patient will understand the implications of this approach.

Attenuated APC is characterized by fewer polyps and a later age of onset. Screening by colonoscopy rather than sigmoidoscopy is appropriate in this syndrome.

HNPCC

Screening for HNPCC involves full colonoscopy for all members of a family who meet the Amsterdam Criteria. Examinations should begin at age 20-25 yr and be done every 2 yr until age 40, and then annually (125, 126, 127, 128, 129). The Amsterdam Criteria are: 1) three relatives with colon cancer, two must be first-degree relatives of the third; 2) colon cancer cases must span two generations; and 3) one case must be diagnosed under the age of 50 yr. The modified Amsterdam Criteria are now favored and are identical, except that other cancers common to HNPCC can be substituted in meeting the criteria (130). These include endometrial, ovarian, pancreatic, gastric, small bowel, and urinary tract cancers.

Genetic testing is also now available for HNPCC and, like FAP, is best applied in families that are clinically known to have the disease, i.e., meet the Amsterdam Criteria (131). Testing is applied in the clinical setting exactly like in FAP in that an index case is found for initial testing. In HNPCC, the index case would preferably be the youngest diagnosed case available. Also as in FAP, once the disease-causing mutation is found in the index case, other family members can be tested with near 100% accuracy, both positive and negative. These results can then guide who should actually have screening. Unlike FAP, however, mutations are presently found in only about half of index cases from Amsterdam Criteria-positive families. Thus, genetic testing is not helpful in half of the families, and all members of such families need the requisite colonoscopy screening. The difficulty in HNPCC genetic testing is further increased as multiple genes are involved, fewer labs do the testing, and the testing is more expensive.

A most important question is how (or if) to apply genetic testing to families with a strong family history of colon cancer, but the Amsterdam Criteria are not met. HNPCC mutations are found in only 8% of such families. One suggested approach that is gaining popularity is to examine the colon cancer tissue from the index case for microsatellite instability (MSI) (132). The presence of MSI indicates frequent genetic mutations throughout the genome. This is a feature of virtually all colon cancers from HNPCC patients, but only of about 15% of sporadic colon cancers. MSI testing is simple, inexpensive, and can be done on fresh, frozen, or even microscopic slide tissue from colon cancers. The clinical approach is to do MSI testing on tumor tissue from an index case in the family in question. If MSI is negative, HNPCC is effectively ruled out. If positive, one can proceed to genetic testing, with a substantial higher likelihood than 8% of finding an HNPCC mutation.

The difficulty with this approach is that only a few commercial labs are beginning to do MSI testing, and the clinician can spend considerable time with logistics. It is thus now strongly encouraged that both Amsterdam Criteria-positive families and families with a strong family history (but Criteria-negative) be referred to a regional high-risk colon cancer program. Genetic counseling, MSI testing, and mutation finding can then be done and interpreted. A genetic or clinical diagnosis and screening recommendations will be formulated by these centers, and the patients can then be returned to their referring physician for management.

Strong Family History of Colon Cancer: Multiple First-Degree Relatives With Colorectal Cancer, or a Single First-Degree Relative With Cancer (Diagnosed) at Age <60 yr

A history of either multiple first-degree relatives with colorectal cancer, or first-degree relatives diagnosed under age 60, predicts a higher lifetime incidence of colorectal cancer (133, 134, 135, 136, 137) and a higher yield of colonoscopic screening (138). The overall colon cancer risk is three to four times that of the general population. Screening should be performed by colonoscopy, beginning at age 40 or 10 yr younger than age at diagnosis of the youngest affected relative (Table 2). The recommended interval for colonoscopy is 3-5 yr. Most patients can be examined at 5-yr intervals, but the recommendation allows clinicians to adjust the interval for stronger family histories. There is some evidence that persons with a first-degree relative with adenoma have an increased incidence of colorectal cancer (139, 140). However, because patients with only small tubular adenomas do not themselves incur an increased risk of colorectal cancer, it is difficult to understand how a history of only small tubular adenomas would predict an increased risk of colorectal cancer in one's relatives. A history of first-degree relatives with adenomas with advanced pathology or adenomas diagnosed at age <60 yr is more likely to be significant, but this issue has not been studied adequately and information on

relatives' adenoma type is usually not clinically available. Screening recommendations for patients with these family histories may be individualized, and specific recommendations are discussed further in the revised ACG polyp guideline (141). This group with a strong family history of colon cancer may in some cases be considered for MSI testing as outlined above.

Moderately Increased Risk: Single First-Degree Relative With Colorectal Cancer Diagnosed at Age >60 yr

For persons with a single first-degree relative diagnosed with colorectal cancer at age 60 yr, there is an approximate two times greater risk of colon cancer than that observed in the general population. Furthermore, the risk for colon cancer at age 40 yr is the same as the risk in the general population at age 50 yr (142). Thus, in this risk group, the recommendations are the same as for average-risk persons, but screening should begin at age 40 rather than age 50. For persons with a family history of first-degree relative with adenomas at age 60 yr, screening recommendations should be individualized.

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Table 2. ACG Recommendations for Screening in Persons With a Positive Family History That Does Not Meet or Approach the Modified Amsterdam Criteria for HNPCC

History:	Recommendation
Single first degree relative with colorectal cancer diagnosed at age 60 yr	<ul style="list-style-type: none"> • Begin screening at age 40 • Preferred screening: colonoscopy every 10 yr
Single first-degree relative with colorectal cancer diagnosed at age <60 yr or multiple first-degree relatives with colorectal cancer	<ul style="list-style-type: none"> • Begin screening at age 40 or 10 yr younger than age of diagnosis of the youngest affected relative, whichever is first • Preferred screening: colonoscopy every 3-5 yrs

ACG = American College of Gastroenterology; HNPCC = hereditary non-polyposis colorectal cancer.

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