American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008

Douglas K. Rex, MD, FACG[1], David A. Johnson, MD, FACG[1], Joseph C. Anderson, MD[1], Phillip S. Schoenfeld, MD, MSEd, MSc (Epi), FACG[1], Carol A. Burke, MD, FACG[1] and John M. Inadomi, MD, FACG[1]

This document is the first update of the American College of Gastroenterology (ACG) colorectal cancer (CRC) screening recommendations since 2000. The CRC screening tests are now grouped into cancer prevention tests and cancer detection tests. Colonoscopy every 10 years, beginning at age 50, remains the preferred CRC screening strategy. It is recognized that colonoscopy is not available in every clinical setting because of economic limitations. It is also realized that not all eligible persons are willing to undergo colonoscopy for screening purposes. In these cases, patients should be offered an alternative CRC prevention test (flexible sigmoidoscopy every 5–10 years, or a computed tomography (CT) colonography every 5 years) or a cancer detection test (fecal immunochemical test for blood, FIT).

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INTRODUCTION

The members of the writing committee carried out a systematic literature review and developed the updated guideline recommendation document. Only peer-reviewed English language articles were included. The criteria used for evaluation of studies and assessment of the category of evidence and strength of recommendation are shown in **Table 1** (1). These guidelines have also been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees.

The ACG is an organization of more than 10,000 clinical gastroenterologists and related health professionals. In 2000, the ACG issued colorectal cancer (CRC) screening recommendations that endorsed colonoscopy every 10 years, beginning at age 50, as the preferred CRC screening strategy (2). The ACG was the first organization to recommend colonoscopy as the preferred strategy for the CRC screening; and the American Society for Gastrointestinal Endoscopy (3) and National Comprehensive Cancer Network (4) subsequently endorsed this recommendation.

Other guidelines for CRC screening often utilize an approach called the "menu of options." In this approach, multiple options for screening are presented which differ with regard to their effectiveness, risk, and degree of invasiveness (and, therefore, potentially their acceptability to patients). The menu-of-options approach was first formalized by the "GI consortium" in May 1997 (5), endorsed by the American Cancer Society in 1997 (6), revised by the US Multisociety Task Force in 2003 (7), and revised by a joint committee of the US Multisociety Task Force, the American Cancer Society, and the American College of Radiology in 2008 (8). The ACG participated in and endorsed the menu-of-options approach in 1997, 2003, and 2008. The ACG continues to endorse the menu-of-options approach as appropriate to CRC screening. Publication of this guideline does not rescind the ACG's endorsement of the joint guideline (8). New recommendations, which differ from the earlier ACG guideline, are highlighted in **Table 2**. The rationale for a separate ACG screening guideline is discussed below.

Rationale for a preferred strategy

As in 2000, the ACG recommends that clinicians have access to a "preferred" strategy for making CRC screening recommendations, as an alternative to the "menu of options" approach, if warranted by the performance characteristics of one of the tests. The ACG recommends colonoscopy every 10 years based on the evidence of colonoscopy effectiveness, cost-effectiveness, and acceptance by patients. A "preferred" strategy simplifies and shortens discussions with patients and could also increase the likelihood that screening is offered to patients. One randomized trial showed that patients were more likely to undergo screening with the "preferred" strategy approach compared with the "menu of options" (9). Another study found no improvement in screening rates when multiple options were presented (10). Maintaining simplicity in guidelines may have value, in that recent evidence has suggested that practi-

[1]Indiana University Medical Center, Gastroenterology, IU Hospital, Indianapolis, USA. **Correspondence:** Douglas K. Rex, MD, FACG, Indiana University Medical Center, Gastroenterology, 550 N University Blvd., IU Hospital, #4100, Indianapolis 46202, USA. E-mail: drex@iupui.edu
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Table 1. Grading recommendations

Grade of recommendation/ description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A/Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT, randomized controlled trial.

Source: Guyatt *et al.* (1).

Table 2. Changes in this guideline from the 2000 ACG recommendations for screening (see reference 2)

1. Screening tests are divided into cancer prevention and cancer detection tests. Cancer prevention tests are preferred over detection tests.
2. Screening is recommended in African Americans beginning at age 45 years.
3. CT colonography every 5 years replaces double contrast barium enema as the radiographic screening alternative, when patients decline colonoscopy.
4. FIT replaces older guaiac-based fecal occult blood testing. FIT is the preferred cancer detection test.
5. Annual Hemoccult Sensa and fecal DNA testing every 3 years are alternative cancer detection tests.
6. A family history of only small tubular adenomas in first-degree relatives is not considered to increase the risk of CRC.
7. Individuals with a single first-degree relative with CRC or advanced adenomas diagnosed at age ≥60 years can be screened like average-risk persons.

ACG, American College of Gastroenterology; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test.

tioners often do not follow recommended intervals for postpolypectomy surveillance, which may in part be because of their complexity (11–13). The ACG acknowledges that listing quality colonoscopy as a "preferred" CRC prevention strategy places greater emphasis on effectiveness than on risk. Current trends in procedure use in the United States reflect and are consistent with the ACG's recommendation of colonoscopy as the preferred strategy for CRC screening, in that colonoscopy procedure volumes have risen dramatically, whereas flexible sigmoidoscopy and double-contrast barium enema (DCBE) procedure volumes have decreased precipitously, and fecal occult blood test (FOBT) has decreased modestly (14).

Cancer prevention tests vs. cancer detection tests

The recent joint guideline (8) groups CRC screening tests into cancer prevention and cancer detection tests. Cancer prevention tests have the potential to image both cancer and polyps, whereas cancer detection tests have low sensitivity for polyps and typically lower sensitivity for cancer compared with that in cancer prevention tests (imaging tests). The ACG supports the division of screening tests into cancer prevention and cancer detection tests, but recommends a preferred cancer prevention test—colonoscopy every 10 years (Grade 1 B) and a preferred cancer detection test—annual fecal immunochemical test (FIT) to detect occult bleeding (Grade 1 B). All recommendations in this guideline are provided in **Table 3**.

Preferred CRC prevention test: colonoscopy every 10 years (Grade 1 B)

The ACG recommends that quality colonoscopy be offered first to patients aged ≥50 years (**Table 3**). A background discussion of screening colonoscopy, including discussion of quality in technical performance (which is deemed critical to screening

Table 3. CRC screening recommendations

Preferred CRC screening recommendations
• Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1 B) Screening should begin at age 45 years in African Americans (Grade 2 C)
• Cancer detection test. This test should be offered to patients who decline colonoscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1 B)
Alternative CRC prevention tests
• Flexible sigmoidoscopy every 5–10 years (Grade 2 B)
• CT colonography every 5 years (Grade 1 C)
Alternative cancer detection tests
• Annual Hemoccult Sensa (Grade 1 B)
• Fecal DNA testing every 3 years (Grade 2 B)
Recommendations for screening when family history is positive but evaluation for HNPCC considered not indicated
• Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥60 years
Recommended screening: same as average risk (Grade 2 B)
• Single first-degree with CRC or advanced adenoma diagnosed at age <60 years or two first-degree relatives with CRC or advanced adenomas.
Recommended screening: colonoscopy every 5 years beginning at age 40 years or 10 years younger than age at diagnosis of the youngest affected relative (Grade 2 B)
FAP
• Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counseling and genetic testing, if they have siblings or children who could potentially benefit from this testing (Grade 2 B)
• Patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed) should undergo annual flexible sigmoidoscopy or colonoscopy, as appropriate, until such time as colectomy is deemed by physician and patient as the best treatment (Grade 2 B)
• Patients with retained rectum after subtotal colectomy should undergo flexible sigmoidoscopy every 6–12 months (Grade 2 B)
• Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. Patients with 10–100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MYH associated polyposis (Grade 2 C)
HNPCC
• Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumor or a family member's tumor and/or tumor immunohistochemical staining for mismatch repair proteins (Grade 2 B)
• Patients with positive tests can be offered genetic testing. Those with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at age 20–25 years, until age 40 years, then annually thereafter (Grade 2 B)

CRC, colorectal cancer; CT, computed tomography, FAP, familial adenomatous polyposis; FIT, fecal immunochemical test; HNPCC, hereditary non-polyposis colorectal cancer.

colonoscopy) is found in Appendix B. Alternative CRC prevention tests are discussed in Appendix C. In clinical settings, in which economic issues preclude primary screening with colonoscopy, or for patients who decline colonoscopy, one of the alternative cancer prevention tests (**Table 3**, Appendix C) or the preferred cancer detection test, occult blood detection through the FIT (**Table 3**) should be offered.

Preferred cancer detection test: annual FIT (Grade 1 B)

The preferred cancer detection test is annual FIT. This test has superior performance characteristics when compared with older guaiac-based Hemoccult II cards (15–17); additionally, there were 10 and 12% gains in adherence with the FIT in the first two randomized controlled trials comparing the FIT with guaiac-based testing (18,19), The overall result of superior performance and improved adherence was a doubling in the detection of advanced lesions, with little loss of positive predictive value (18,19). The ACG supports the joint guideline recommendation that older guaiac-based fecal occult blood testing be abandoned as a method for CRC screening. Alternatives, such as the higher sensitivity guaiac-based Hemoccult Sensa and the fecal DNA test (**Table 3**), are discussed in Appendix D. However, because of more extensive data (compared with Hemoccult Sensa), and the high cost of fecal DNA testing, the ACG recommends the FIT as the preferred cancer detection test (Grade 1 B).

Age to begin screening in average-risk persons

The ACG continues to recommend that screening begin at age 50 years in average-risk persons (i.e., those without a family history of colorectal neoplasia) (Grade 1 B), except for African Americans. The ACG recommends that screening begin at age 45 years in African Americans (Grade 2 C). The rationale for this recommendation has been presented elsewhere (20).

The "average risk" population is large and complex with regard to risk. Certain other subgroups of the average-risk population might warrant initiation of screening at an earlier or later age, depending on their risk. For example, the age-adjusted risk of incident cancers (21) and prevalent adenomas (22–25) is greater in men than in women. However, delaying the onset of screening in women could result in a greater loss of life years in women who develop CRC in their 50s compared with that in men, as women on average live longer than men. Pending further study and evaluation of this issue, the ACG recommends that screening begin at age 50 years for both the genders (at age 45 years for African-American men and women).

In reviewing the literature, the writing committee also identified heavy cigarette smoking and obesity as linked to an increased risk of CRC and to the development of CRC at an earlier age. The clinical evidence supporting the increased risk in these groups is given in Appendix A. The current evidence supports a decision by clinicians in individual patients with an extreme smoking history or obesity to begin screening at an age earlier than 50 years and perhaps as early as 45 years. A formal recommendation to begin screening at an earlier age in smokers and obese patients will be re-evaluated as additional evidence appears.

Family history screening

Single first-degree relative with CRC or advanced adenoma (adenoma ≥1 cm in size, or with high-grade dysplasia or villous elements) diagnosed at age ≥60 years.

Recommended screening: same as average risk (colonoscopy every 10 years beginning at age 50 years) (Grade 2 B).

Single first-degree relative with CRC or advanced adenoma diagnosed at age <60 years or two first-degree relatives with CRC or advanced adenomas.

Recommended screening: colonoscopy every 5 years beginning at age 40, or 10 years younger than age at diagnosis of the youngest affected relative (Grade 2 B).

The ACG recommendations for modification of the screening approach, according to family histories of colorectal polyps and cancer that are not suggestive of the Hereditary Non-polyposis Colorectal Cancer, are summarized in **Table 3**. Justification for these recommendations was outlined in the 2000 guideline (2). The major change in this guideline is that an increased level of screening is no longer recommended for a simple family history of adenomas in a first-degree relative. The earlier ACG recommendations were that adenomas and cancer in first-degree relatives be treated equally in modifying the family history. Many studies purporting to describe the risk of CRC in first-degree relatives of patients with adenomas could be considered to have evaluated the reverse risk, i.e., the risk of adenomas in first-degree relatives of patients with CRC. In particular, case–control studies addressing this issue have often delivered an odds ratio (rather than a true risk ratio) that describes the "risk of adenomas among relatives of a patient with colorectal cancer" instead of the "risk of colorectal cancer among relatives of a patient with adenoma(s)." A single study carried out colonoscopies in first-degree relatives of patients with large adenomas, and found these relatives to have an increased risk of either large adenomas or cancer (26). There are no similar studies carried out in first-degree relatives of patients with small tubular adenomas. It is well known that persons with only small tubular adenomas (<1 cm) and only low-grade dysplasia are not at an increased risk for developing CRC (27). From a genetic perspective, it makes little sense that their relatives should be considered at an increased risk. Recently, some studies have identified an extremely high prevalence of small tubular adenomas in screening populations (28). Continuation of the recommendation to screen first-degree relatives of patients with only small tubular adenomas could result in most of the population being screened at age 40, with doubtful benefit. From a practical perspective, many clinicians have found that patients are often not aware of whether their first-degree relatives had advanced adenomas vs. small tubular adenomas, or whether their family members had non-neoplastic vs. neoplastic polyps. Given these difficulties, the ACG now recommends that adenomas only be counted as equal to a family history of cancer when there is a clear history, or medical report containing evidence, or other evidence to indicate that family members had advanced adenomas (an adenoma ≥1 cm in size, or with high-grade dysplasia, or with villous elements). Patients without information on the nature of polyps in a family member can be encouraged to pursue such information, but because of confidentiality requirements, pursuit of such information by the treating physicians is typically not feasible.

Familial adenomatous polyposis

Patients with features of an inherited CRC syndrome should be advised to pursue genetic counseling and, if appropriate, genetic testing. Genetic counseling and informed consent are preferred over direct genetic testing, as current laws may not provide adequate protection with regards to life insurance, long-term care insurance, or disability insurance. Individuals with familial adenomatous polyposis (FAP) should undergo APC mutation testing and, if negative, MYH mutation testing. Patients with FAP or at risk of FAP based upon family history should undergo annual flexible sigmoidoscopy or colonoscopy, as appropriate, until such time when colectomy is deemed by both physician and patient as the best treatment (29). Patients with a retained rectum after total colectomy and ileorectal anastomosis, ileal pouch, after total proctocolectomy and ileal-pouch anal anastomosis, or stoma after total proctocolectomy and end ileostomy, should undergo endoscopic assessment approximately every 6–12 months after surgery, depending on the polyp burden seen (Grade 2 B). Individuals with oligopolyposis (<100 colorectal polyps) should be sent for genetic counseling, consideration of APC and MYH mutation testing, and individualized colonoscopy surveillance depending on the size, number, and pathology of polyps seen (Grade 2 C). Upper endoscopic surveillance is recommended in individuals with FAP or MAP (MYH-associated polyposis).

Hereditary non-polyposis colorectal cancer

Patients who meet the Bethesda criteria for hereditary non-polyposis colorectal cancer (30) should undergo microsatellite instability testing of their tumor, or an affected family member's tumor, and/or tumor immunohistochemical staining for mismatch repair proteins. Patients with positive tests can be offered genetic testing and when genetic testing is positive in a proband, at risk family members can be offered genetic testing. Those patients with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at age 20–25 years, until age 40 years, then annually thereafter (Grade 2 B).

SUMMARY OF CURRENT GUIDELINE UPDATES

Owing to its potential for a high level of effectiveness in CRC prevention and extensive study of outcomes associated with its use, quality colonoscopy every 10 years beginning at age 50 remains the preferred CRC screening strategy. Patients who decline colonoscopy, or for whom colonoscopy is unavailable, or not feasible should be offered one of the alternative CRC prevention tests (flexible sigmoidoscopy every 5–10 years or computed tomography, CT, colonography every 5 years) or the

preferred CRC detection test (FIT). The CRC screening in average-risk persons should begin at age 50, except that in African Americans, screening should begin at age 45 years. A family history of polyps need not invoke earlier onset of screening or other adjustment in screening, unless there is convincing evidence that the polyps were advanced adenomas.

REFERENCES

1. Guyatt G, Gutterman D, Baumann MH *et al.* Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest 2006;129:174–81.
2. Rex DK, Johnson DA, Lieberman DA *et al.* Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. Am J Gastroenterol 2000;95:868–77.
3. Davila RE, Rajan E, Baron TH *et al.* ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc 2006;63:546–57.
4. Colorectal Cancer Screening. NCCN Clinical Practice Guidelines in Oncology. http:\\www.nccn.org (V.2.2008).
5. Winawer S, Fletcher R, Miller L *et al.* Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997;112:594–642.
6. Byers T, Levin B, Rothenberger D *et al.* American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: update 1997. American Cancer Society Detection and Treatment Advisory Group on Colorectal Cancer. CA: Cancer J Clin 1997;47:154–60.
7. Winawer S, Fletcher R, Rex D, *et al.*, Gastrointestinal Consortium P. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology 2003;124:544–60.
8. Levin B, Lieberman DA, McFarland B *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570–95.
9. Inadomi J, Kuhn L, Vijan S *et al.* Adherence to competing colorectal cancer screening strategies. Am J Gastroenterol 2005;100:S387–8.
10. Griffith JM, Lewis CL, Brenner AR *et al.* The effect of offering different numbers of colorectal cancer screening test options in a decision aid: a pilot randomized trial. BMC Med Inform Decis Mak 2008;8:4; Available at http://www.biomedcentral.com/1472-6947/8/4.
11. Boolchand V, Olds G, Singh J *et al.* Colorectal screening after polypectomy: a national survey study of primary care physicians. Ann Intern Med 2006;145:654–9.
12. Mysliwiec PA, Brown ML, Klabunde CN *et al.* Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. Ann Intern Med 2004;141:264–71.
13. Burke C, Issa M, Chruch J. A nationwide survey of post-polypectomy surveillance colonoscopy: too many too soon!. Gastroenterology 2005;128:A566.
14. Robertson RH, Burkhardt JH, Powell MP *et al.* Trends in colon cancer screening procedures in the US Medicare and Tricare populations: 1999–2001. Prev Med 2006;42:460–2.
15. Nakajima M, Saito H, Soma Y *et al.* Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. Br J Cancer 2003;89:23–8.
16. Lee KJ, Inoue M, Otani T *et al.* Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: a prospective cohort study in Japan. Cancer Detect Prev 2007;31:3–11.
17. Zappa M, Castiglione G, Grazzini G *et al.* Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. Int J Cancer 1997;73:208–10.
18. van Rossum LG, van Rijn AF, Laheij RJ *et al.* Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82–90.
19. Hol L, van Leerdam ME, van Ballegooijen M *et al.* Attendance to screening for colorectal cancer in the Netherlands; randomized controlled trial comparing two different forms of faecal occult blood tests and sigmoidoscopy. Gastroenterology 2008;134:A87.
20. Agrawal S, Bhupinderjit A, Bhutani MS *et al.* Colorectal cancer in African Americans. Am J Gastroenterol 2005;100:515–23; discussion 514.
21. Chu KC, Tarone RE, Chow WH *et al.* Temporal patterns in colorectal cancer incidence, survival, and mortality from 1950 through 1990. J Natl Cancer Inst 1994;86:997–1006.
22. Schoenfeld P, Cash B, Flood A *et al.* Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005;352:2061–8.
23. Lieberman DA, Weiss DG, Bond JH *et al.* Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000;343:162–8.
24. Regula J, Rupinski M, Kraszewska E *et al.* Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355:1863–72.
25. Rex D, Sledge G, Harper P *et al.* Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. Am J Gastroenterol 1993;88:825–31.
26. Cottet V, Pariente A, Nalet B *et al.* Colonoscopic screening of first-degree relatives of patients with large adenomas: increased risk of colorectal tumors. Gastroenterology 2007;133:1086–92.
27. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658–62.
28. Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42–7.
29. Vasen HF, Moslein G, Alonso A *et al.* Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704–13.
30. Umar A, Boland CR, Terdiman JP *et al.* Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261–8.
31. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2001;10:725–31.
32. Driver JA, Gaziano JM, Gelber RP *et al.* Development of a risk score for colorectal cancer in men. Am J Med 2007;120:257–63.
33. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults–United States, 2006. MMWR Morb Mortal Wkly Rep 2007;56:1157–61.
34. Giovannucci E, Colditz GA, Stampfer MJ *et al.* A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst 1994;86:192–9.
35. Giovannucci E, Rimm EB, Stampfer MJ *et al.* A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 1994;86:183–91.
36. Heineman EF, Zahm SH, McLaughlin JK *et al.* Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. Int J Cancer 1994;59:728–38.
37. Newcomb PA, Storer BE, Marcus PM. Cigarette smoking in relation to risk of large bowel cancer in women. Cancer Res 1995;55:4906–9.
38. Paskett ED, Reeves KW, Rohan TE *et al.* Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. J Natl Cancer Inst 2007;99:1729–35.
39. Slattery ML, Potter JD, Friedman GD *et al.* Tobacco use and colon cancer. Int J Cancer 1997;70:259–64.
40. Sturmer T, Glynn RJ, Lee IM *et al.* Lifetime cigarette smoking and colorectal cancer incidence in the Physicians' Health Study I. J Natl Cancer Inst 2000;92:1178–81.
41. Terry P, Ekbom A, Lichtenstein P *et al.* Long-term tobacco smoking and colorectal cancer in a prospective cohort study. Int J Cancer 2001;91:585–7.
42. Chao A, Thun MJ, Jacobs EJ *et al.* Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. J Natl Cancer Inst 2000;92:1888–96.
43. Colangelo LA, Gapstur SM, Gann PH *et al.* Cigarette smoking and colorectal carcinoma mortality in a cohort with long-term follow-up. Cancer 2004;100:288–93.
44. Messina CR, Kabat GC, Lane DS. Perceptions of risk factors for breast cancer and attitudes toward mammography among women who are current, ex- and non-smokers. Women Health 2002;36:65–82.
45. Buc E, Kwiatkowski F, Alves A *et al.* Tobacco smoking: a factor of early onset of colorectal cancer. Dis Colon Rectum 2006;49:1893–6.
46. Michalek AM, Cummings KM. The association between cigarette smoking and age at cancer diagnosis. Hum Biol 1987;59:631–9.
47. Zisman AL, Nickolov A, Brand RE *et al.* Associations between the age at diagnosis and location of colorectal cancer and the use of alcohol and tobacco: implications for screening. Arch Intern Med 2006;166:629–34.
48. Campbell RJ, Ferrante JM, Gonzalez EC *et al.* Predictors of advanced stage colorectal cancer diagnosis: results of a population-based study. Cancer Detect Prev 2001;25:430–8.

49. Anderson JC, Attam R, Alpern Z *et al.* Prevalence of colorectal neoplasia in smokers. Am J Gastroenterol 2003;98:2777–83.
50. Lieberman DA, Prindiville S, Weiss DG *et al.* Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 2003;290:2959–67.
51. Limburg PJ, Vierkant RA, Cerhan JR *et al.* Cigarette smoking and colorectal cancer: long-term, subsite-specific risks in a cohort study of postmenopausal women. Clin Gastroenterol Hepatol 2003;1:202–10.
52. Slattery ML, Curtin K, Anderson K *et al.* Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J Natl Cancer Inst 2000;92:1831–6.
53. Anderson JC, Alpern Z, Messina CR *et al.* Predictors of proximal neoplasia in patients without distal adenomatous pathology. Am J Gastroenterol 2004;99:472–7.
54. Martinez ME, Reid M, Jiang R *et al.* Accuracy of self-reported smoking status among participants in a chemoprevention trial. Prev Med 2004;38:492–7.
55. Adams KF, Leitzmann MF, Albanes D *et al.* Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol 2007;166:36–45.
56. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr 2007;86:556–65.
57. Anderson JC, Messina CR, Dakhllalah F *et al.* Body mass index: a marker for significant colorectal neoplasia in a screening population. J Clin Gastroenterol 2007;41:285–90.
58. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. World J Gastroenterol 2007;13:4199–206.
59. Bergstrom A, Pisani P, Tenet V *et al.* Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001;91:421–30.
60. Gunter MJ, Leitzmann MF. Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. J Nutr Biochem 2006;17:145–56.
61. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109S–20S.
62. Bird CL, Frankl HD, Lee ER *et al.* Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am J Epidemiol 1998;147:670–80.
63. Shinchi K, Kono S, Honjo S *et al.* Obesity and adenomatous polyps of the sigmoid colon. Jpn J Cancer Res 1994;85:479–84.
64. Neugut AI, Lee WC, Garbowski GC *et al.* Obesity and colorectal adenomatous polyps. J Natl Cancer Inst 1991;83:359–61.
65. John BJ, Irukulla S, Abulafi AM *et al.* Systematic review: adipose tissue, obesity and gastrointestinal diseases. Aliment Pharmacol Ther 2006;23:1511–23.
66. Rondinone CM. Adipocyte-derived hormones, cytokines, and mediators. Endocrine 2006;29:81–90.
67. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 2001;60:329–39.
68. Amemor S, Ootani A, Fujise T *et al.* Adipocytes and preadipocytes promote the proliferation of colon cancer cells *in vitro*. Am J Physiol Gastrointest Liver Physiol 2007;292:G923–9.
69. Hoda MR, Keely SJ, Bertelsen LS *et al.* Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. Br J Surg 2007;94:346–54.
70. El-Serag HB. Esophagus and colon disease. Gastroenterol Clin North Am. In: Johnson DA (ed). Obesity and the Gastroenterologist. 2005;34:63–82.
71. Thiis-Evensen E, Hoff G, Sauar J *et al.* Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999;34:414–20.
72. Mandel JS, Church TR, Bond JH *et al.* The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603–7.
73. Winawer SJ, Zauber AG, Ho MN *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–81.
74. Citarda F, Tomaselli G, Capocaccia R *et al.* The Italian Multicentre Study Group. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48:812–5.
75. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995;123:904–10.
76. Brenner H, Chang-Claude J, Seiler CM *et al.* Does a negative screening colonoscopy ever need to be repeated? Gut 2006;55:1145–50.
77. Gross CP, Andersen MS, Krumholz HM *et al.* Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer. JAMA 2006;296:2815–22.
78. Sedjo RL, Byers T, Barrera E Jr *et al.* A midpoint assessment of the American Cancer Society challenge goal to decrease cancer incidence by 25% between 1992 and 2015. CA Cancer J Clin 2007;57:326–40.
79. Selby JV, Friedman GD, Quesenberry CP Jr *et al.* A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653–7.
80. Newcomb PA, Storer BE, Morimoto LM *et al.* Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst 2003;95:622–5.
81. Seeff LC, Manninen DL, Dong FB *et al.* Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? Gastroenterology 2004;127:1661–9.
82. Rex DK, Chak A, Vasudeva R *et al.* Prospective determination of distal colon findings in average-risk patients with proximal colon cancer. Gastrointest Endosc 1999;49:727–30.
83. Jass JR. Hyperplastic polyps and colorectal cancer: is there a link? Clin Gastroenterol Hepatol 2004;2:1–8.
84. Leard LE, Savides TJ, Ganiats TG. Patient preferences for colorectal cancer screening. J Fam Pract 1997;45:211–8.
85. Zubarik R, Ganguly E, Benway D *et al.* Procedure-related abdominal discomfort in patients undergoing colorectal cancer screening: a comparison of colonoscopy and flexible sigmoidoscopy. Am J Gastroenterol 2002;97:3056–61.
86. Gatto NM, Frucht H, Sundararajan V *et al.* Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003;95:230–6.
87. Levin TR, Zhao W, Conell C *et al.* Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145:880–6.
88. Rex DK, Petrini JL, Baron TH *et al.* Quality indicators for colonoscopy. Am J Gastroenterol 2006;101:873–85.
89. Rex DK. Have we defined best colonoscopic polypectomy practice in the United States? Clin Gastroenterol Hepatol 2007;5:674–7.
90. Pabby A, Schoen RE, Weissfeld JL *et al.* Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005;61:385–91.
91. Farrar WD, Sawhney MS, Nelson DB *et al.* Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006;4:1259–64.
92. Lieberman DA, Weiss DG, Harford WV *et al.* Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133:1077–85.
93. Rex DK, Cummings OW, Helper DJ *et al.* 5-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons [see comment]. Gastroenterology 1996;111:1178–81.
94. Avidan B, Sonnenberg A, Schnell TG *et al.* New occurrence and recurrence of neoplasms within 5 years of a screening colonoscopy. Am J Gastroenterol 2002;97:1524–9.
95. Imperiale TF, Glowinski EA, Lin-Cooper C *et al.* Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med 2008;359:1218–24.
96. Burke CA, Elder K, Lopez R. Screening for colorectal cancer with flexible sigmoidoscopy: is a 5-yr interval appropriate? A comparison of the detection of neoplasia 3 yr vs. 5 yr after a normal examination. Am J Gastroenterol 2006;101:1329–32.
97. Schoen RE, Pinsky PF, Weissfeld JL *et al.* Results of repeat sigmoidoscopy 3 years after a negative examination. JAMA 2003;290:41–8.
98. Singh H, Turner D, Xue L *et al.* Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006;295:2366–73.
99. Singh G, Gerson LB, Wang H *et al.* Screening colonoscopy, colorectal cancer and gender: an unfair deal for the fair sex? Gastrointest Endosc 2007;65:AB100.
100. Sawhney MS, Farrar WD, Gudiseva S *et al.* Microsatellite instability in interval colon cancers. Gastroenterology 2006;131:1700–5.
101. Arain M, Sheikh S, Thaygarajan B *et al.* Molecular markers of rapidly growing tumors: another piece to the puzzle. Am J Gastroenterol 2008;103:S200.
102. Rex DK, Bond JH, Winawer S *et al.* Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002;97:1296–308.
103. Rex DK. Maximizing detection of adenomas and cancers during colonoscopy. Am J Gastroenterol 2006;101:2866–77.

104. Barclay RL, Vicari JJ, Doughty AS *et al.* Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533–41.
105. Chen SC, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. Am J Gastroenterol 2007;102:856–61.
106. Rex DK, Rahmani EY, Haseman JH *et al.* Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997;112:17–23.
107. Bressler B, Paszat LF, Chen Z *et al.* Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007;132:96–102.
108. Singh H, Turner D, Xue L *et al.* Colorectal cancers after a negative colonoscopy. Gastroenterology 2007;132:A149.
109. Alberts DS, Martinez ME, Roe DJ *et al.* Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med 2000;342:1156–62.
110. Schatzkin A, Lanza E, Corle D *et al.* Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000;342:1149–55.
111. Robertson DJ, Greenberg ER, Beach M *et al.* Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005;129:34–41.
112. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003;58:76–9.
113. Froehlich F, Wietlisbach V, Gonvers JJ *et al.* Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc 2005;61:378–84.
114. Jain S, Johnson WD, Minocha A. Impact of quality of bowel preparation on the detection of colonic polyps during colonoscopy: a prospective study. Gastroenterology 2007;132:A315.
115. Cohen L, Kastenberg D, Lottes SR *et al.* Polyp detection rate during colonoscopy is correlated with quality of bowel preparation. Am J Gastroenterol 2006;101:S556.
116. Parra-Blanco A, Nicolas-Perez D, Gimeno-Garcia A *et al.* The timing of bowel preparation before colonoscopy determines the quality of cleansing, and is a significant factor contributing to the detection of flat lesions: a randomized study. World J Gastroenterol 2006;12:6161–6.
117. Rostom A, Jolicoeur E, Dube C *et al.* A randomized prospective trial comparing different regimens of oral sodium phosphate and polyethylene glycol-based lavage solution in the preparation of patients for colonoscopy. Gastrointest Endosc 2006;64:544–52.
118. Aoun E, Abdul-Baki H, Azar C *et al.* A randomized single-blind trial of split-dose PEG-electrolyte solution without dietary restriction compared with whole dose PEG-electrolyte solution with dietary restriction for colonoscopy preparation. Gastrointest Endosc 2005;62:213–8.
119. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. Anesthesiology 1999;90:896–905.
120. Wexner SD, Beck DE, Baron TH *et al.* A consensus document on bowel preparation before colonoscopy: prepared by a Task Force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Surg Endosc 2006;20:1161.
121. Rockey DC, Paulson E, Niedzwiecki D *et al.* Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet 2005;365:305–11.
122. Johnson CD, MacCarty RL, Welch TJ *et al.* Comparison of the relative sensitivity of CT colonography and double-contrast barium enema for screen detection of colorectal polyps. Clin Gastroenterol Hepatol 2004;2:314–21.
123. Johnson CD, Chen MH, Toledano AY *et al.* Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;359:1207–17.
124. Pickhardt P, Choi J, Hwang I. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349:2191–200.
125. Johnson CD, Harmsen WS, Wilson LA *et al.* Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. Gastroenterology 2003;125:311–9.
126. Rex DK, Lieberman D. ACG colorectal cancer prevention action plan: update on CT-colonography. Am J Gastroenterol 2006;101:1410–3.
127. Brenner DJ, Georgsson MA. Mass screening with CT colonography: should the radiation exposure be of concern? Gastroenterology 2005;129:328–37.
128. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.
129. Hur C, Chung DC, Schoen RE *et al.* The management of small polyps found by virtual colonoscopy: results of a decision analysis. Clin Gastroenterol Hepatol 2007;5:237–44.
130. Imperiale TF, Ransohoff DF, Itzkowitz SH *et al.* Fecal DNA vs. fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004;351:2704–14.
131. Ahlquist D, Sargent DJ, Levin TR *et al.* Stool DNA screening for colorectal cancer: prospective multicenter comparison with hemoccult. Gastroenterology 2005;128:A63.
132. Whitney D, Skoletsky J, Moore K *et al.* Enhanced retrieval of DNA from human fecal samples results in improved performance of colorectal cancer screening test. J Mol Diagn 2004;6:386–95.
133. Itzkowitz SH, Jandorf L, Brand R *et al.* Improved fecal DNA test for colorectal cancer screening. Clin Gastroenterol Hepatol 2007;5:111–7.

APPENDIX A

Risk factors under consideration for more intense screening in future guidelines (smokers and obese patients)

The ACG recommends that clinicians be aware of an increased risk of CRC in cigarette smokers and obese patients. This evidence is summarized below. The ACG does not recommend that screening be initiated earlier in these groups at this time. Clinicians should make special efforts to ensure that screening takes place in these groups. The ACG recommends additional study to characterize the potential benefits, harms, and cost-effectiveness of earlier screening in these groups.

Cigarette smokers

Smoking is associated with up to 20% of all CRCs in the United States (31), and was one of the strongest predictors of CRC in the Physician's Health Study (32). As over 20% of Americans currently smoke (33), the increase in risk for CRC may be yet another major medical consequence of tobacco use within the United States and worldwide. Literature review reveals that people who have more than 20 pack-years of smoking have over 2–3 times the risk for colorectal adenomas as non-smokers (31). There is as much as a 30% increased risk for colon and rectal cancer in male and female smokers (34–41), and smoking may account for 12% of deaths from CRC (42,43). Smokers have perceptions which may decrease their likelihood to be screened (44).

An important observation that underscores the potential value of screening smokers earlier is the younger age at which smokers are diagnosed with CRC. Although there may be other factors that explain this observation, an age difference of at least 5 years between smokers and non-smokers with CRC has been noted in four separate populations over two decades (45–47). Smokers may also be more likely to present with an advanced stage of CRC than non-smokers (48). Two studies of patients undergoing screening colonoscopy showed that smoking was

associated with a two-fold increase in risk for advanced neoplasia, similar or greater than that of having a first-degree relative with CRC (49,50). Although many studies show a predilection for distal colorectal neoplasia in smokers (34,35,47), the Iowa Women's Health Study showed that female smokers had a higher risk for proximal CRCs (51). This observation may be explained by an increase in microsatellite instability in smokers (52). Anderson *et al.* (53) observed that smokers are at a risk for advanced isolated proximal neoplasia, underscoring the need for complete colonic evaluation in smokers during colonoscopy.

Smoking can be measured by duration, intensity, and number of years since cessation. It has been shown that smokers recall details of their exposure quite accurately (54). Several studies have suggested that smoking one pack per day or more significantly increases the risk and mortality for CRC (38–43). It has also been observed that the risk of CRC (40) and mortality (42) may be increased after 20 pack-years or less of smoking exposure. The impact of quitting is as yet unclear, but it appears that the risk may continue to increase, perhaps as long as 20 years after smoking cessation (34,35,37–39,42).

Based on these data, the ACG recommends that special efforts be made to ensure that screening takes place in active smokers and those who have smoked for more than 20 pack-years. Initiation of screening at a younger age (as early as 45 years) may be shown to be beneficial and cost-effective in persons with more 20 pack-years of smoking. These recommendations, however, may be tempered by the presence of medical complications of smoking that reduce the impact of CRC screening on overall life expectancy. Additional study is warranted.

Obesity

A consistent body of evidence supports the concept that both overweight and obese statuses are associated with an increased risk of CRC. The risk of CRC for obese patients compared with that for non-obese patients is increased by 1.5–2.8 fold (55–60).

Recent data from the NIH–AARP cohort found that body mass index (BMI) was related to CRC risk for younger (age 50–66 years) but not older (age 67–71 years) persons (60). The BMI was associated with an increased incidence of colon cancer in men and women but not with rectal cancer. For men, the relative risks for overweight (BMI 25–30) ranged from 1.44 to 1.53 and for obese (BMI >30–<40) from 1.57 to 2.39, respectively. Corresponding relative risks for women were 1.29–1.31 and 1.13–1.49, respectively. A meta-analysis of six studies estimated a 3% increase (95% CI, 2–4) in CRC risk per one unit increase in BMI (59). The pattern of fat distribution is important as it relates to the reported CRC risk. Abdominal obesity is a stronger risk factor than truncal obesity or BMI (59,61).

Obesity is also associated with colon adenomas (presence and size) (62–64). Overall, obesity approximately doubles the relative risk of adenomas, and is particularly associated with high-risk adenomas (≥1 cm, tubulovillous). The mechanisms by which obesity may promote colon carcinogenesis are discussed elsewhere (65–70).

Based on the apparent increased relative risks for CRC and adenomas, the ACG recommends that special efforts are warranted to ensure the screening takes place in obese and overweight patients. Initiation of screening at an earlier age (as early as 45 years) may be beneficial and cost-effective in obese patients. These recommendations, however, may be tempered by the presence of medical complications of obesity, which reduce the impact of CRC screening on overall life expectancy. Additional study is warranted.

APPENDIX B

Discussion of screening colonoscopy

The evidence that colonoscopy prevents incident CRCs and reduces the consequent mortality from CRC is indirect but substantial. No prospective randomized controlled trial, comparing colonoscopy with no screening, has been carried out. However in a randomized controlled trial, involving only 800 patients, in which flexible sigmoidoscopy with colonoscopy carried out for any polyp detected was compared with no screening, the screening strategy resulted in an 80% reduction in the incidence of CRC (71). In addition, at the University of Minnesota, a randomized controlled trial was carried out comparing annual vs. biennial fecal occult blood testing with rehydration with no screening. Screening resulted in a 20% incidence reduction in CRC, which appeared to have resulted from detection of large adenomas by fecal occult blood testing and subsequent colonoscopy and polypectomy (72). Cohort studies involving patients, who have undergone colonoscopy and polypectomy with apparent clearance of colonic neoplasia, have shown a 76–90% reduction in the incidence of CRC in comparison with reference populations (73,74). Case–control studies of colonoscopy showed a 50% reduction in mortality from CRC in a US Veterans Administration population (75), and there was an 80% reduction in the CRC incidence in the German population (76). Population-based studies in the United States have associated increases in the use of colonoscopy with earlier and more favorable stages in CRC presentation (77), and with reductions in the incidence of CRC (78). Additional evidence for a benefit from colonoscopy screening is extrapolated from case–control studies of sigmoidoscopy, which have shown mortality and incidence reductions of distal CRC of 60 (79) and 80% (80), respectively, in screening populations.

Major advantages of colonoscopy as a screening test include that it is widely available (81), examines the entire colon, allows single-session diagnosis and treatment, is comfortable when carried out with sedation, and is the only test recommended at 10-year intervals (2–8). The incremental benefit of colonoscopy over sigmoidoscopy is the detection of patients with proximal colon neoplasia (particularly advanced adenomas), as well as large hyperplastic polyps that are not associated with distal neoplasia (82,83). Overall, sigmoidoscopy detects 60–70% of the significant neoplasia detected by complete colonoscopy (23). The preference of most American patients is for highly effective

strategies (84), as well as for strategies that provide high levels of comfort and thereby increase the chance that patients will return for additional testing (85). These are important rationales for the use of colonoscopy rather than sigmoidoscopy.

Screening colonoscopy can be associated with significant harm, particularly colonic perforation (86,87). Many perforations are related to polypectomy and because small polyps are so numerous, small polyp polypectomy perforations contribute substantially to the overall perforation risk (87). Perforations associated with removal of small polyps are unfortunate, because the overwhelming majority of these polyps will not harm patients. Effective removal of these polyps by cold snare polypectomy or biopsy techniques is possible, at least for very small polyps (88), and is not associated with either bleeding or perforation. In general, there are insufficient data available from randomized controlled trials to guide or mandate particular polypectomy techniques (89). Pending such trials, the ACG recommends that colonoscopists consider carefully the polypectomy techniques they utilize for small polyps with an aim to reduce the burden of perforation. On the other hand, the ACG acknowledges that use of effective polypectomy techniques is critical for adequate resection of larger polyps. Two studies have suggested that about one-quarter of incident cancers occurring after colonoscopy result from ineffective polypectomy (90,91). Overall, the perforation risk and the requirement for thorough bowel preparation are the major downsides of colonoscopy.

The ACG continues to recommend that colonoscopy be carried out at 10-year intervals in average-risk persons with normal initial examinations. The evidence to support the 10-year interval is indirect but substantial. First, the protective effect for distal CRC provided by sigmoidoscopy and polypectomy in case–control studies, although imperfect, has been shown to be prolonged (79,80). In the Kaiser Permanente case–control study (this study first established the benefit of endoscopic screening), the duration of mortality reduction was 10 years (79). In a recent study of flexible sigmoidoscopy, the duration of protection was 16 years (80). Observational data, in which colonoscopy has been carried out at an initial baseline examination and then was repeated 5 years later, showed a very low yield of advanced adenomas (92–95). Cost analyses of colonoscopy as a screening test for CRC have found cost-effectiveness at equal or greater levels than other screening strategies with a 10-year interval (5). Recent studies in which follow-up sigmoidoscopies were carried out after initial negative examinations (96,97), and population-based studies of symptomatic individuals with negative colonoscopies (98,99) have established that some patients present shortly after negative examinations with cancers or advanced adenomas. What is not clear is the interval at which a second examination would have to be carried out in order to alter the outcome in these cases. Thus, in the population-based study of symptomatic patients with negative colonoscopies in Manitoba, many patients with interval cancers presented in the first few years after the negative colonoscopy, and it is not clear that a second planned examination at 5 years would have altered the outcome. In addition, some biologic variation in the growth rates of tumors, (which is best established for tumors with microsatellite instability or the CpG Island Methylator Phenotype), contributes to the appearance of cancers shortly after negative examinations (100,101). There is little evidence that performing a second examination at 5 years can impact substantially the incidence of these cancers.

Despite these caveats, there is little doubt that the overall impact of colonoscopy depends critically on high-quality baseline examinations. Therefore, the ACG recommends that screening colonoscopies be carried out by appropriately trained and skilled examiners, who are dedicated to consistent performance of high-quality examinations and employ programmatic measurements to optimize the outcomes through continuous quality improvement processes (88,102).

The ACG has both endorsed (102) and developed (88) quality indicators for colonoscopy. Readers can consult these documents (88,102) for a full description of quality indicators for colonoscopy. A major focus of these quality indicators that bears importantly on the impact of colonoscopy at 10-year intervals, are those directed to the quality of mucosal inspection. In addition to using an appropriate technique and time for mucosal inspection, colonoscopists must have expertise in safe and effective bowel preparation. Mucosal inspection during screening colonoscopy should be meticulous. The examiner should perform a slow and obsessive examination, designed to expose all of the colonic mucosa and identify and remove the smallest and flattest adenomas and proximal colon hyperplastic polyps. Several studies have shown that colonoscopists vary dramatically in their detection rates of adenomas (103), and in two recent studies, colonoscopists were shown to differ substantially in their detection of large adenomas (104,105). Colonoscopists in clinical practice should measure their individual adenoma detection rates in the continuous quality improvement process. One or more adenomas should be detected in at least 25% of men aged ≥50 years and 15% of women aged ≥50 years (88,102). These recommendations are derived from screening colonoscopy studies (88,102). In addition, endoscopists should measure their withdrawal times by noting the time of cecal intubation and termination of the examination. These withdrawal times should average at least 6 min in normal colonoscopies, in which no biopsy or polypectomy is carried out. This recommendation is not meant to imply that every colonoscopic withdrawal must last 6 min, as some colons can be examined effectively in <6 min. Furthermore, future research may revise the optimal mean withdrawal time that represents quality colonoscopy. The ACG also recommends that in institutions in which endoscopists from multiple specialties practice, that clinical gastroenterologists should establish institution-wide continuous quality improvement programs, designed to enhance the mucosal inspection performance of all specialties. In particular, three major studies have now identified that colonoscopy by primary care physicians is more likely to result in missed CRC compared with the performance by gastroenterologists (106–108).

The rationale and importance of the continuous quality improvement programs is emphasized by recent studies, showing lower than anticipated rates of protection against CRC by colonoscopy and polypectomy. Thus, adenoma cohorts participating in dietary intervention trials in the United States (109,110) and chemoprevention trials (111) have experienced little or no reduction in CRC incidence, compared with that in general population risk. Although the risk in these cohorts might be anticipated to be higher than the general population, the observed incidence of cancer clearly exceeds that anticipated based on earlier cohort studies (73,74). Population-based studies have confirmed a reduction in the incidence of CRC associated with negative colonoscopy, but the reduction in incidence has been less than anticipated (98,99). In the Manitoba study, the reduction in incidence was < 50% for the first 5 years after the index negative colonoscopy and increased to 72% at 10 years (98). This suggests that significant numbers of lesions present at the index colonoscopy were not detected.

Inadequate bowel preparation is common in the United States (112), and inadequate preparation has been shown to impair the detection of both small (112,113) and large (113) polyps, and has also been shown recently in prospective colonoscopy studies to correlate with polyp detection (114–116). Although several commercial bowel preparations are available, certain principles of preparation will enhance the effectiveness of each of these commercial preparations. Best established is the principle of "splitting," in which at least half of the preparation is given on the day of the colonoscopy (116–118). When all of the bowel preparation is given on the day before examination and the interval between the last dose of preparation and the performance of colonoscopy is prolonged, the probability of poor preparation increases dramatically, particularly in the cecum and ascending colon (116–118). Splitting can be carried out with oral dosing of either polyethylene glycol (116,118) or sodium phosphate (116,117) preparations. The practice guidelines of the American Society of Anesthesiologists allow ingestion of clear liquids until 2 h before sedation (119). Recent guidelines for an effective and safe preparation are available (120), and have particularly emphasized the importance of aggressive hydration before and during the preparation, during the procedure, and after the procedure, especially when using oral sodium phosphate preparations (120).

Several recent technical developments can enhance the mucosal inspection process during colonoscopy. Pancolonic chromoendoscopy is effective for enhancing adenoma detection, but impractical for routine use (103). Narrow band imaging does not enhance mucosal inspection by endoscopists with high adenoma detection rates, but may be a useful teaching tool for enhancement of flat lesion detection by endoscopists with low adenoma detection rates (103). Wide-angle colonoscopy, cap-fitted colonoscopy, and the Third Eye Retroscope (Avantis Medical Systems, Sunnyvale, CA) are all under development as techniques to improve exposure of hidden mucosa during colonoscopy (103). The ACG recommends that clinical gastroenterologists follow actively the technical developments pertaining to mucosal inspection enhancement techniques and incorporate such techniques into practice, as they are proven to be both effective and practical. However, endoscopists should understand that no enhancement technique replaces the need for a meticulous inspection. Elements critical to high-quality mucosal inspection during colonoscopy and which should be incorporated into all colonoscopy practices are detailed in **Table 4**.

Table 4. Key measures for improving the quality and cost-effectiveness of colonoscopy as a CRC screening test

- Bowel preparation should be given in split doses (half of the dose is given on the day of procedure).
- Cecal intubation should be documented by description of landmarks and photography.
- All colonoscopists should document adenoma detection rates.
- Withdrawal times should average at least 6 min in intact colons, in which no biopsies or polypectomies are performed; this has greatest relevance to colonoscopists with low adenoma detection rates.
- Polyps should be removed by effective techniques, including snaring (rather than forceps methods) for all polyps >5 mm in size.
- Piecemeal resection of large sessile lesions requires close follow-up.
- In patients with complete examinations and adequate preparation, recommended screening and surveillance intervals should be followed.

CRC, colorectal cancer.

Although colonoscopy is widely available and reimbursed as a strategy for CRC prevention, in some health care systems economic factors place limits on the feasibility of screening colonoscopy. In such cases, or when patients decline colonoscopy, alternative CRC prevention tests or FIT are very acceptable alternatives (**Table 3**).

APPENDIX C

Alternative cancer prevention tests

Alternative CRC prevention tests are listed in **Table 3**. The rationale for flexible sigmoidoscopy as a CRC screening test was reviewed in the 2000 guideline. Since that time, the use of flexible sigmoidoscopy has declined dramatically in the United States (14), though its use is still prevalent in certain settings. Flexible sigmoidoscopy is fundamentally similar to colonoscopy, except that less of the colon is examined, bowel preparation on average is less effective, and patients are not sedated. Flexible sigmoidoscopy can be offered at either 5-year or 10-year intervals. In the past, flexible sigmoidoscopy has typically been recommended at 5-year intervals, and this approach may be best if the extent of the examination is limited, or if the examination is carried out by an individual with limited endoscopic skills. However, the protective effect of sigmoidoscopy is long (79,80). Furthermore, colonoscopy may have more protection against left-sided compared with right-sided colon

cancers (99,101). Therefore, flexible sigmoidoscopy is carried out by highly skilled practitioners, it may be recommended at 10-year, rather than 5-year intervals (8).

Double contrast barium enema is no longer recommended as an alternative CRC prevention test, because its use has declined dramatically and also as its effectiveness for polyp detection is less than computed tomography (CT) colonography. The ACG considers that the DCBE could be used as a CRC screening test that is within the standard of care, if it is carried out by high volume operators with special interest and expertise in the technique. The rationale for DCBE over CT colonography is its low cost, but patients clearly prefer CT colonography (121,122). Only a few centers in the United States still perform sufficient volumes of screening DCBE to warrant its continued use.

CT colonography, every 5 years, is endorsed as an alternative to colonoscopy every 10 years because of its recent performance in the American College of Imaging Network Trial 6664 (also known as the National CT Colonography Trial) (123). Results from earlier multicenter trials in the United States ranged from excellent (124) to poor (121,125). The principle performance feature that justifies inclusion of CT colonography as a viable alternative in patients who decline colonoscopy, is that the sensitivity for polyps ≥1 cm in size in the most recent multicenter US trial was 90% (123). In this study, 25% of radiologists who were tested for entry into the trial but performed poorly were excluded from participation, and thus lower sensitivity might be expected in clinical practice. The CT colonography probably has a lower risk of perforation than colonoscopy in most settings, but for several reasons it is not considered the equivalent of colonoscopy as a screening strategy. First, the evidence to support an effect of endoscopic screening on prevention of incident CRC and mortality is overwhelming compared with that for CT colonography (see Appendix B). Second, the inability to detect polyps 5 mm and smaller, which constitutes 80% of colorectal neoplasms, and whose natural history is still not understood, necessitates performance of the test at 5-year, rather than 10-year intervals (8). This is likely to increase overall costs, if CT colonography is used as a primary strategy. Although management of polyps < 1 cm in size is controversial, the ACG continues to recommend that patients with polyps 6 mm or larger be referred for polypectomy, as should patients with three or more polyps of any size read with high confidence (126). Polyps ≤5 mm in size interpreted with high confidence should be described in the CT colonography report (126). Unfortunately, false positives are common, and the specificity for polyps ≥1 cm in size in the National CT Colonography Trial was only 86%, with a positive predictive value of 23% (123). Thus, colonoscopy for polyps detected on CT colonography will often require long procedures, in order to verify absence of other polyps. False positives diminish cost-effectiveness by increasing follow-up colonoscopies and repeat CT colonographies to verify false positive status. The ACG recommends that asymptomatic patients be informed of the possibility of radiation risk associated with one or repeated CT colonography studies, though the exact risk associated with radiation is unclear (127,128). The value of extracolonic findings detected by CT colonography is mixed, with substantial costs associated with incidental findings, but occasional important extracolonic findings are detected such as asymptomatic cancers and large abdominal aortic aneurysms. As a final point, the ACG is also concerned about the potential impact of CT colonography on adherence and thus on polypectomy rates. Thus, if CT colonography substantially improves adherence, it should improve polypectomy rates and thereby reduce CRC, even if only large polyps are detected and referred for colonoscopy. On the other hand, if CT colonography largely displaces patients who would otherwise be willing to undergo colonoscopy, then polypectomy rates will fall substantially, which could significantly increase the CRC incidence (129). Thus, for multiple reasons, and pending additional study, CT colonography should be offered to patients who decline colonoscopy.

APPENDIX D

Alternative cancer detection tests

The alternative cancer detection tests are listed in **Table 3**. Hemoccult Sensa is an improved guaiac-based card for fecal occult blood testing. It has superior sensitivity to older guaiac-based cards, but the overall evidence is less than that supporting the FIT. Furthermore, the FIT resulted in improved adherence for CRC screening over card-based tests in two randomized controlled trials (18,19). Therefore, FITs are preferred over Hemoccult Sensa.

Fecal DNA testing has been evaluated in three different versions. The first (Version 1.0) included tests for point mutations in *k-ras*, APC, P53, mutations in the BAT26 microsatellite instability marker, and the DNA integrity assay. The sensitivity for cancer was superior to traditional guaiac-based occult blood testing, but the absolute sensitivity was 52% and disappointing considering the high cost of the test (130). After completion of the trial, it was learned that the DNA integrity assay, which had appeared to be the most promising element in the assay in early studies (131), was non-informative because of the instability of DNA during shipment. Subsequently, Version 1.1 has been commercialized, which includes the same DNA test used in Version 1.0, but includes technical improvements of gel-based DNA capture and buffer stabilization of long or redundant DNA critical to the DNA integrity assay. No screening test using Version 1.1 has been reported, but a trial in established CRCs identified 70% sensitivity and specificity of ~95%, (specificity similar to Version 1.0) (132). Version 2.0 utilizes a simplified assay consisting of the DNA integrity assay and hypermethylation of the vimentin gene. No screening trial with Version 2.0 has been carried out, but a study in established CRCs shows sensitivity of 87% for cancer, but specificity fell to 82% (133). The latter specificity limits the frequency with which the test can be carried out reasonably. Given that the performance characteristics of the FIT are approximately equal to Versions 1.0, and 1.1, and superior to Version 2.0 with regard to specificity, and that FIT costs much less than fecal DNA testing,

there is no rationale for primary use of fecal DNA testing as a CRC detection test. The value of combining FIT and fecal DNA testing is unknown. Additional disadvantages of fecal DNA testing include no established data on which to determine an optimal interval, and the lack of clinical recommendations on how to respond to patients who have positive DNA tests and negative colonoscopies. Although the recent guideline endorsing fecal DNA testing declined to recommend an interval for DNA testing, the ACG considers that testing at intervals <3 years would be cost prohibitive.