REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review of the Recent Literature

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Colorectal cancer (CRC) remains a major clinical and public health challenge, with 148,810 new cases and 49,960 deaths expected in the United States in 2008.[1] The field of CRC research is dynamic and expanding in several directions, encompassing areas of clinical and outcomes research, epidemiology, public health, and molecular sciences. In this review, we summarize important developments in CRC screening and surveillance over the past several years and discuss the present state of the art of this field.

Risk Factors for Colorectal Neoplasia

Metabolic Syndrome

According to the National Cholesterol Education Program's Adult Treatment panel III, metabolic syndrome is the presence of 3 or more of the following factors: hypertension (blood pressure of 130/85 mm Hg or greater), central adiposity (waist circumference greater than 102 cm in men or greater than 88 cm in women or a body mass index [BMI] greater than 27 [kg/m^2]), low high-density lipoprotein (HDL) cholesterol (HDL <40 mg/dL in men or <50 mg/dL in women), hypertriglyceridemia (150 mg/dL or greater), and impaired glucose tolerance (fasting serum glucose of 110 mg/dL or greater).[2] Colorectal neoplasia has been associated with markers of glucose and insulin control; insulin resistance, which is the cornerstone of the metabolic syndrome, may be the mechanism by which several risk factors (obesity, diabetes mellitus, [lack of] fitness) affect colorectal carcinogenesis.[3,4]

Four of the most recent studies of metabolic syndrome and CRC are summarized in Table 1.[5–8] These studies comprise different study populations and different study designs but use the same or comparable definitions of metabolic syndrome, similar methods of analysis, and either adenoma or cancer as outcomes. The study findings are quite consistent: either the metabolic syndrome or its components increase the risk for colorectal neoplasia (both adenomas and cancer) by approximately 50%. The effect of metabolic syndrome on neoplasia risk appears to be greater in men than in women. The relationship between metabolic syndrome and large bowel location of neoplasia reported by Chiu et al[6] is interesting and requires validation in analyses of other populations.

Cigarette Smoking

The epidemiologic evidence that cigarette smoking increases the risk of CRC was elegantly reviewed by Giovannucci in 2001.[9] An association between colorectal neoplasia and cigarette smoking is supported by several studies, with the association more consistently established for smoking and adenomas, including large adenomas, than for cancer.[9–24] Recently, the bulk of the evidence supports an association with CRC as well. With men having begun smoking several decades earlier than women, the temporal pattern of the studies supports an induction period of 3–4 decades between exposure and the diagnosis of CRC.[9] Despite the volume of studies, several questions remain unanswered: What is the relationship between dose and duration and risk of neoplasia? Which persons are most susceptible to the effects of cigarette smoking? Is smoking associated to specific subgroups of cancer, perhaps having one or more prevalent mutations? By how much and how quickly does risk drop after quitting smoking?

Table 2 summarizes recent selected endoscopic and population-based studies on smoking and risk for colorectal neoplasia.[25–29] The 5 studies use different study designs: cohort, case-control, and cross-sectional, with sample sizes ranging from 1154 to 146,877 individuals. All 5 use multivariable analysis, which provides the inde-

Abbreviations used in this paper: CAD, coronary artery disease; CCSA, colon cancer-specific antigen; CTC, computed tomographic colonography; FDR, first-degree relative; gFOBT, guaiac-based fecal occult blood testing; HNPCC, hereditary nonpolyposis CRC; iFOBTs, immunochemical fecal occult blood tests; MMR, mismatch repair; MSI, microsatellite instability.

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Table 1. Summary of Selected Studies on Metabolic Syndrome and Risk of Colorectal Neoplasia

First author, year (ref)	Study population	Study design	Criteria for metabolic syndrome	Outcomes	Type of risk model	Main findings
Ahmed, 2006 (5)	14,109 subjects from the Atherosclerosis Risk in Communities (ARIC) multicenter study)	Cohort	ATP III	Colorectal cancer	Multiple logistic model, adjusted for age, gender, family history of CRC, physical activity, NSAID use, aspirin use, smoking, alcohol use, hormone replacement use	MS associated with increased risk of CRC (age and gender adjusted RR, 1.49; 95% CI: 1.0–2.4), which attenuated after multivariate adjustment (RR, 1.39; 95% CI: 0.9–2.2). Adjusted risk was increased in men (RR, 1.78; 95% CI: 1.02–3.6) but not in women (RR, 1.16; 95% CI: 0.6–2.2)
Sturmer, 2006 (8)	22,071 healthy male physicians initially ages 40–84 years	Cohort	BMI of ≥27 kg/m², total cholesterol of ≥240 mg/dL or use of lipid-lowering drugs, blood pressure of ≥130/85 mm Hg or use of antihypertensives, and a diagnosis of diabetes mellitus	Colorectal cancer	Multiple logistic model, adjusted for age, smoking, exercise, alcohol use, multivitamin use, and consumption of fruits and vegetables	BMI >27 kg/m² (RR, 1.4; 95% CI: 1.1–1.7) and diabetes (RR, 1.5; 95% CI: 1.1–2.0) were associated with CRC; hypertension and hypercholesterolemia were not.
Kim, 2007 (7)	3584 consecutive subjects undergoing screening colonoscopy	Cross-sectional	Modified ATP III criteria	Colorectal adenoma	Multiple logistic model, adjusted for age, gender, smoking, alcohol use	17% of subjects with adenomas and 11% of those without adenomas had MS. MS associated with increased risk of adenoma: OR, 1.51; 95% CI: 1.19–1.93. Waist circumference was an independent risk factor for adenoma: OR, 1.39; 95% CI: 1.15–1.68
Chiu, 2007 (6)	4277 consecutive ethnic Chinese who had screening or surveillance colonoscopy as part of a medical health checkup	Cross-sectional	Modified ATP III criteria, modified Asian criteria (HDL cholesterol of <40 mg/dL, waist circumference ≥90 cm for men, ≥80 cm for women)	Colorectal neoplasia, anatomic location	Multiple logistic model, adjusted for age, gender, BMI, smoking, alcohol use, previous adenoma, family history of CRC	MS associated with increased risk of any neoplasia (OR, 1.35; 95% CI: 1.05–1.73), proximal neoplasia (OR, 1.62; 95% CI: 1.14–2.30), synchronous lesions (OR, 2.15; 95% CI: 1.40–3.31), and synchronous lesions both proximal and distal (OR, 2.30; 95% CI: 1.42–3.72).

MS, metabolic syndrome.

pendent effect of smoking after adjustment for covariates such as age, sex, BMI, and others.

The study by Lieberman et al, a colonoscopy-based study, examined the effect of several candidate risk factors on the risk of advanced neoplasia in a cohort of 3121 asymptomatic patients aged 50–75 years from 13 Veterans Affairs medical centers.[27] Using a multivariate model that included family history of CRC, BMI, physical activity, smoking, alcohol use, and several dietary components, the investigators found that the effect of smoking on advanced neoplasia (odds ration [OR], 1.85; 95% confidence interval [CI]: 1.33–2.58) was comparable with having a first-degree relative (FDR) with CRC (OR, 1.66; 95% CI: 1.16–2.35). In a retrospective, cross-sectional analysis of 1988 persons undergoing screening colonoscopy, Anderson et al found that cigarette smoking increased the risk for any colorectal neoplasia (OR, 1.89; 95% CI: 1.42–2.51) and for significant neoplasia (OR, 2.26; 95% CI: 1.56–3.27) that was predominantly left-sided.[26]

Results of recent population-based studies have shown somewhat inconsistent results. The findings of the case-control study by Verla-Tebit et al are consistent with those of several earlier epidemiologic studies that support the 30–35 year induction period between exposure to cigarette smoking and CRC.[29] The results also suggest that risk reduction requires at least 20 years and increases with increasing duration of smoking cessation. In addition to the findings described in Table 2, the study by Akhter et al, which studied only men, found that longer smoking duration, age of 18 or younger at onset of smoking, and consumption of 20 or more cigarettes per day significantly increased the risk of CRC, with risk ratios ranging from 1.46 to 1.86.[25]

In the study from the Women's Health Initiative,[28] which is a pooled analysis of participants in the observational study and 3 clinical trials, the risk of rectal cancer was increased with longer smoking duration and its confounder, older age at smoking cessation; however, the risk of colon cancer was not increased. This study has limitations, including self-reported smoking exposure that did not allow for changes in smoking behavior after initial reporting and a rate of cigarette smoking that was lower than US women of similar ages.

In summary, the majority of evidence indicates that CRC is a tobacco-associated malignancy. In the United States, it has been estimated that as many as 1 in 5 CRCs is attributable to cigarette smoking.[11,13,14,20] The magnitude of the increase in risk for CRC and large adenoma appears to be the same as having an FDR with CRC. It would be useful to have a way to estimate

Table 2. Summary of Selected Studies on Cigarette Smoking and Risk of Colorectal Neoplasia

First author, year (ref)	Study population	Study design	Outcomes	Type of risk model	Main findings
Lieberman, 2003 (27)	3121 asymptomatic patients aged 50-75 years from 13 Veterans Affairs medical centers	Cross-sectional	Advanced neoplasia (CRC or advanced polyps)	Multiple logistic regression that adjusted for age, family history, BMI, physical activity, alcohol use, NSAID use, certain dietary features	Current smoking was a risk factor for advanced neoplasia (OR, 1.85; 95% CI: 1.33-2.85) and was of comparable magnitude to having an FDR with CRC (OR, 1.66; 95% CI: 1.16–2.35).
Anderson, 2003 (26)	1988 persons aged 40 and older undergoing screening colonoscopy	Cross-sectional	Significant neoplasia (CRC, advanced polyps, or >2 adenomas of any size)	Multiple logistic regression that adjusted for age, alcohol consumption, exercise, BMI, ethnicity, education, and consumption of fruits and vegetables	Current smokers were more likely to have any neoplasia (OR, 1.89; 95% CI, 1.42–2.51) and significant neoplasia (OR, 2.26; 95% CI: 1.56–3.27). Risk of significant neoplasia was greater for smokers than for those with a family history of CRC.
Verla-Tebit, 2006 (29)	540 patients with incident CRC and 614 population-based, matched to cases by 5-year age group, sex, county of residence	Case-control	CRC	Multiple logistic model that adjusted for age, sex, history of CRC in first-degree relatives, BMI, alcohol use, physical activity, fruit and vegetable intake, red meat consumption, NSAID use, previous endoscopy of the large bowel, education level, and use of hormone replacement therapy	Compared with nonsmokers, smokers for ≥40 years had increased risk (OR, 1.92; 95% CI: 1.13–3.28). Among smokers ≥30 years, risk was greater among women (OR, 3.5; 95% CI: 1.29–9.52) than men (OR, 1.15; 95% CI: 0.69–1.91). Risk reduction observed after ≥20 years of quitting smoking and was significant for ≥40 years (OR, 0.46; 95% CI: 0.21–0.98).
Akhter, 2007 (25)	25,279 Japanese men recruited when aged 40-64 years	Cohort (7 years of follow-up)	CRC	Proportional hazards model that adjusted for age, family history of CRC, education, BMI, alcohol use, time spent walking per day, and consumption frequency of fruits, green-yellow vegetables, and red meat	Compared with never smokers, the risk of CRC was increased for past smokers (RR, 1.73; 95% CI: 1.04–2.87) and current smokers (RR, 1.47; 95% CI: 0.93–2.34). Among current smokers, a greater number of cigarettes smoked per day and an earlier age of smoking onset were associated with a significant linear increase in CRC risk.
Paskett, 2007 (28)	146,877 women's Health Initiative participants	Cohort (mean of 7.8 years of follow-up)	CRC	Proportional hazards model that adjusted for age, ethnicity, study type (observational or clinical trial) study arm, family history of CRC, total physical activity metabolic equivalents, alcohol use, NSAID use, hormone therapy use, colonoscopy, diabetes, waist circumference, certain dietary features	Current smokers had increased risk for rectal cancer (HR, 1.95; 95% CI: 1.10–3.47) but not colon cancer (HR, 1.03; 95% CI: 0.77–1.38).

the incremental effect of smoking on risk of advanced neoplasia that considers sex; age of smoking onset; degree and duration of cigarette consumption; and, for former smokers, time since smoking cessation. Greater consideration should be given to cigarette smoking when considering whether, when, and how best to screen patients.

Coronary Artery Disease

In a study from Hong Kong, Chan et al compared the prevalence of colorectal neoplasia in 206 subjects with angiographically proven coronary artery disease (CAD), 208 subjects whose angiogram did not show CAD, and an age- and sex-matched control group of 207 subjects who were asymptomatic (other than having functional dyspepsia with a normal upper endoscopy) but who did not have angiography.[30] Colonoscopy was scheduled within 8 weeks after eligibility was determined or after revascularization. Endoscopists were blinded to CAD status.

The prevalence of advanced neoplasia in the CAD-positive, CAD-negative, and control groups was 18.4%, 8.7%, and 5.8%, respectively ($P < .001$), whereas the prevalence of cancer was 4.4%, 0.5%, and 1.4%, respectively ($P = .02$). After adjustment for age and sex, CAD remained associated with advanced neoplasia (OR, 2.51; 95% CI: 1.43–4.35). Of interest, both metabolic syndrome and cigarette smoking were strong independent predictive factors for the positive association between CAD and advanced neoplasia, meaning that persons who were smokers and/or had the metabolic syndrome were much more likely to develop both conditions.

Although it is not clear that the CAD-positive group was free of symptoms of signs of early CRC, this study links CAD with advanced neoplasia and is consistent with previously published studies.[31,32] It is unclear whether and to what extent the association would remain after further adjustment for other confounding factors. Nevertheless, most likely because of a common set of risk factors that includes cigarette smoking, waist circumference, diabetes, and others, CAD appears to be a marker for colorectal neoplasia. Although the prevalence of advanced neoplasia in persons with CAD suggests the need for earlier or more aggressive CRC screening, the extent to which CAD as a comorbid condition may reduce the benefits of screening requires careful consideration.

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Diabetes Mellitus

Previous studies have shown that the risk of CRC is higher among persons with diabetes, although this finding is not consistent among studies nor is the contribution of confounding factors to the increased risk well established. In a population-based cohort study, Limburg et al identified incident cases of CRC among 1975 type 2 diabetic individuals and compared them with what was expected from the general population.[33] Overall risk of CRC was increased among diabetic individuals (standardized incidence ratio= 1.39; 95% CI: 1.03–1.82). However, the increased risk was present among men only, both overall (SIR, 1.67; 95% CI: 1.16–2.33) and proximally (SIR, 1.96; 95% CI: 1.16–3.10). Furthermore, current and former cigarette smokers were at higher risk for CRC than diabetic individuals who never smoked.

In addition to increasing baseline risk for colorectal neoplasia, insulin resistance also increases the risk for recurrent neoplasia. In an analysis from the Polyp Prevention Trial, Flood et al compared fasting insulin and glucose levels in 375 subjects with and 375 subjects without recurrent adenoma.[34] After adjustment for age, sex, BMI, and intervention group, risk for recurrent adenoma was higher for subjects in the highest quartile compared with the lowest quartile: OR, 1.56; 95% CI: 1.00–2.43 for insulin; OR, 1.49; 95% CI: 0.95–2.31 for glucose. The highest quartile of glucose was associated with advanced adenoma as well: OR, 2.43; 95% CI: 1.23–4.79. The strength of the associations between high fasting glucose and risk of recurrent adenoma increased when the analysis was restricted to subjects with no family history of CRC.

These studies support other research in which diabetes has been associated with increased risk for CRC and are consistent with a larger body of literature that links insulin resistance, metabolic syndrome, and coronary artery disease with colorectal neoplasia. Understanding both the mechanisms leading to neoplasia and the independent contribution of each of these factors to advanced adenoma and CRC risks requires further study.

Although the literature is replete with data on risk factors for CRC and adenoma, most established risk factors are not incorporated into current screening guidelines. Current guidelines stratify risk with age and family history alone. Age is used only as a threshold factor, although CRC incidence increases with age in an approximately linear fashion. The risk of CRC in average-risk persons doubles by 10 years—approximately the same increase in risk as having an FDR with CRC.[35] We need a way to integrate all risk factors (age, sex, family history, cigarette smoking, metabolic syndrome, and others) quantitatively to estimate absolute risk for CRC and advanced adenoma. One study has integrated age, sex, and BMI to estimate the risk of advanced neoplasia anywhere in the large intestine.[36] Another study used age, sex, and most advanced distal finding to estimate the risk of advanced proximal neoplasia.[37] Both systems require validation and further development before they can be applied to clinical practice. Furthermore, the effect of more extensive risk stratification on screening remains to be determined. On the one hand, providing risk-specific information to patients and providers has the potential to improve screening rates and screening efficiency. On the other hand, if risk stratification is perceived as making CRC screening too complicated, there is the potential to adversely affect further uptake of screening. Whether incorporating several factors with modest relative risks would add significantly to using age, sex, and family history alone is also important to determine.

Screening Colonoscopy

Several recent studies have described the findings of screening colonoscopy in an asymptomatic average-risk population.[38–43] Table 3 summarizes the study characteristics of this body of literature. Although the study objectives, settings, and designs vary, the variation does not necessarily preclude comparing the findings.

Descriptively, the studies are from Japan, Poland, Israel, Korea, and the United States. The number of persons analyzed varies from 994 to 43,042. The mean age ranges from 48.2 years in a study in which 57% of subjects were younger than 50 years old, to 62.2 years. The proportion of men ranges from 0% in a screening study of military women to 72% in a Japanese study of asymptomatic adults who participated in a comprehensive health examination.

The endoscopic findings, expressed as the proportion of persons according to the most advanced histology, are shown in Table 4. Despite differences in the study populations, the fraction of persons with no colorectal neoplasia is consistent, ranging from 75% to 83%. Ranges of persons with nonadvanced adenoma, advanced adenoma, and cancer are 8.9%–16.5%, 3%–6.3%, and 0%–1.3%, respectively, with the variation largely because of age and sex.

The prevalence of findings in these recent studies is comparable with previously published screening studies,[26,37,44–47] with the possible exception of VA Cooperative Study No. 380, in which rates of neoplasia were numerically greater, reflecting the high-risk features of the study population, particularly the high predominance of men.[46]

These studies are a reminder that the majority of screening colonoscopies will show no adenomas. They highlight the need to identify a way to estimate absolute risk for individual persons so that screening colonoscopy may be more efficiently targeted to those with advanced neoplasia. Considering these more recent studies in the aggregate, the number of persons required to undergo screening colonoscopy on average is approximately 9 to detect 1 person with 1 or more nonadvanced adenoma,

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Table 3. Description of Screening Colonoscopy Studies

First author (ref)	Year	Study objective	Study population	Study design	Study setting	Recruitment period	Study findings
Schoenfeld (40)	2005	To determine prevalence and location of advanced neoplasia	Consecutive, average risk, asymptomatic women referred for screening[a]	Prospective, cross-sectional	4 Military medical centers	7/1999–12/2002	Advanced neoplasia was distal in 1.7% (n = 25) and proximal in 3.2% (n = 47). Sigmoidoscopy would have detected only 35.2% of advanced neoplasia.
Morikawa (43)	2005	To determine the test characteristics of an immunochemical FOBT	Asymptomatic adults who participated in a comprehensive health examination	Retrospective, cross-sectional	A general hospital and its affiliated clinic	4/1983–3/2002	Sensitivity and specificity of 1-time iFOBT were 65.8% and 94.6%, respectively, for cancer and 27.1% and 95.1%, respectively, for advanced neoplasia.
Lin (38)	2006	To compare estimated life-years saved with screening colonoscopy in very elderly vs younger persons	Consecutive asymptomatic adults undergoing screening colonoscopy in age categories 50–54 years (n = 1034), 75–79 years (n = 147), and >80 years (n = 63)	Prospective, cross-sectional	Tertiary referral single medical center	1/2002–1/2005	Despite higher prevalence of neoplasia in elderly patients, mean extension in life expectancy was much lower in persons aged 80 years or older than in the 50–54-year-old groups (0.13 vs 0.85 years, respectively).
Regula (39)	2006	To derive and validate a model for detection of advanced neoplasia. To quantify the number of persons needed to screen to detect 1 advanced neoplasm	Consecutive, asymptomatic adults age 50-66 years in good general health; and those age 40-49 years with a family history of cancer of any type	Retrospective, cross-sectional	Database from a national colonoscopy-based screening program	10/2000–2004	Advanced neoplasia and to quantify was more prevalent in men in all age groups, with lower numbers needed to screen in men (range, 10–23) than in women (range, 18–36).
Strul (41)	2006	To evaluate the prevalence and anatomic location of adenoma and carcinoma	Consecutive average risk adults who were asymptomatic regarding cancer-related symptoms or alarm signs	Retrospective, cross-sectional	Databases of procedures from 1 of 6 outpatient gastroenterology clinics of a health maintenance organization in Tel-Aviv, Israel	1/1996–2/2001	Prevalence of neoplasia increased with older age. Among persons with neoplasia, 21%–43% had isolated proximal neoplasia (beyond the sigmoidoscope).
Kim (42)	2007	To evaluate the usefulness of colonoscopy to detect polyps	Consecutive adults who voluntarily underwent colonoscopy as part of a health examination program	Retrospective, cross-sectional	Database of a company-based screening colonoscopy program	1/2003–9/2005	Adenomatous polyps were present in 17.9%, advanced adenomas in 3.4%. Adenomas were more prevalent in men (23.6%) than in women (11.5%) and increased with age in both groups.

[a]Includes only persons aged 50 years and older.

23 to detect an advanced adenoma, 20 for advanced neoplasia, and 143 for cancer. One goal of outcomes research in this area should be to identify a cluster of factors that define a subgroup at such low risk for advanced neoplasia that screening may be either deferred or performed confidently with noninvasive testing. Another goal is to identify a high-risk subgroup among "average-risk" persons for which colonoscopy is preferred over other screening tests.

Emerging Screening Modalities

Fecal DNA

The rationale for detecting mutated genes in feces of patients with CRC arose from studies published during the 1990s that established the following: (1) alterations in DNA were fairly neoplasm-specific, (2) colorectal neoplasms shed cells and released DNA continuously, and (3) polymerase chain reaction technology could identify altered DNA in feces. Between 2000 and 2004, several teams of investigators examined a variety of fecal-based genetic markers for colorectal neoplasia.[48–52] Most of these studies were case-control studies that involved an advanced spectrum of CRC. A subgroup of these studies used a 21-component DNA panel where sensitivity for cancer ranged from 62% to 91% and from 27% to 82% for adenomas with a specificity ranging from 93% to 96%.[48,53–55] These studies begged the question of how this panel would perform in the screening setting.

A multicenter study published in 2004 compared the 21-component DNA panel with Hemoccult II among 4404 asymptomatic average-risk subjects.[44] A subgroup of 2507 subjects was analyzed, including all those with CRC and advanced adenomatous polyps plus a random

Table 4. Endoscopic Findings of Recent Screening Studies

First author (ref)	Year	Study No.	Mean age, yr	Gender (% men)	No neoplasia, n (%)	Nonadvanced adenoma, n (%)	Advanced adenoma, n (%)	Advanced neoplasia, n (%)	Adenocarcinoma, n (%)
Schoenfeld (40)	2005	1463	59	0	1164 (79.6)	227 (15.5)	71 (4.9)	72 (4.9)	1 (0.1)
Morikawa (43)	2005	21,805	48.2	72	17,480 (80)	3544 (16)	648 (3)	727 (3.3)	79 (0.4)
Lin (38)	2006	1244	56.2	47	1038 (83)	151 (12.1)	52 (4.2)	55 (4.4)	3 (0.2)
Regula (39)	2006	43,042[a]	Not available	35.7	32,389 (75)	3843 (8.9)	2168 (5.0)	2553 (5.9)	385 (0.9)
Strul (41)	2006	994[a]	62.2	47	766 (77)	156 (15.6)	59 (5.9)	72 (7.2)	13 (1.3)
Kim (42)	2007	4491	48.4	53	3534 (79)	804 (17.9)	153 (3.4)	153 (3.4)	0 (0)

[a]Includes only persons aged 50 years and older.

sample of subjects with no polyps or with small tubular adenomas. The fecal DNA panel detected 16 of 31 cancers as compared with 4 of 31 for Hemoccult II (51.6% vs 12.9%, respectively, $P = .003$). Among 418 subjects with advanced neoplasia, the panel was positive in 76 (18.2%) vs 45 (10.8%) for Hemoccult II ($P = .001$). Among subjects with no polyps, specificity was 94% for the fecal DNA panel and 95% for Hemoccult II.

The results of this multicenter study were disappointing because the sensitivity of the panel was lower than anticipated based on previous studies. The reason for the lower sensitivity was the nearly complete nonfunction of one of the most important components of the panel, the DNA integrity assay. The poor performance of the DNA integrity assay was due to DNA degradation of the long apoptotic DNA shed from neoplastic cells by fecal bacterial endonucleases during overnight delivery of the specimens to the laboratory.

In a subsequent study supported by the same manufacturer, the prototype assay, along with markers of methylation, were tested in 40 subjects with CRC and 122 subjects with a normal colonoscopy.[56] Two improvements were made to the prototype assay: (1) use of a gel-based DNA capture approach, rather than the initial bead-based technology, which enhanced the extraction of DNA from feces; and (2) addition of a DNA-stabilizing buffer to the defecated specimen, which prevented DNA degradation. In addition, a new marker, methylation of the vimentin gene, was tested. Together, these improvements constituted the version 2 assay.

The original panel of markers (version 1) had a sensitivity of 72.5% and specificity of 86.9%, with the DNA integrity assay alone having a sensitivity of 65% and specificity of 93%. The combination of the DNA integrity assay and vimentin gene methylation was considered to be the optimal combination, with a sensitivity of 87.5% and specificity of 82%. This combination of markers maintained its sensitivity across the disease spectrum: stage I (n = 8), 75%; stage II (n = 10), 90%; stage III (n = 17), 94%; and stage IV (n = 5), 80%. Importantly, older age was associated with a higher false-positive rate of vimentin methylation.

The improved sensitivity and lower cost of the assay have improved the overall value of fecal DNA to the point that it may be considered a screening option for persons who are not high-risk and who would otherwise remain unscreened. However, despite the cost reduction of fecal DNA, it remains much more expensive than immunochemical fecal occult blood tests (iFOBTs). In addition, uncertainties regarding fecal DNA include determining an optimal screening interval, estimating its programmatic test characteristics, and determining sensitivity for advanced adenomas. In particular, the programmatic performance of iFOBT may be equal to or superior to fecal DNA with much lower costs.

iFOBT

Guaiac-based fecal occult blood testing (gFOBT) has been an evidence-based mainstay of CRC screening for well over a decade.[57–59] However, it has several limitations including low sensitivity for cancer (and even lower for advanced polyps) and need for periodic testing; gFOBT reacts with nonhuman heme in food as well as blood from the upper gastrointestinal tract. iFOBTs were developed to improve specificity and eliminate the need for dietary restriction because they use one or more monoclonal or polyclonal antibodies to detect human hemoglobin.[60] Over the last few years, several studies indicate that iFOBT is more sensitive than gFOBT for advanced colorectal neoplasia with no difference in specificity.

Morikawa et al published a retrospective analysis of data collected between 1983 and 2002 involving 21,805 asymptomatic adults (mean age, 48 years; 72% men) who underwent one-time iFOBT with the Magstream 1000/Hem SP iFOBT system (Fujirebio, Tokyo, Japan) within 2 days prior to colonoscopy.[43] iFOBT detected 65.8% of all cancers and 27% of all advanced neoplasia, with respective specificities of 94.6% and 95.1%. Sensitivity by Dukes' stage was 50% for Dukes' stage A, 70% for Dukes' stage B, and 78.3% for Dukes' stage C or D. Of interest, the sensitivity of iFOBT was greater for advanced distal neoplasia than for advanced proximal neoplasia (30.7% vs 16.3%, respectively, $P < .001$).

This study is one of the few to have compared a FOBT with the reference standard of colonoscopy.[43] Although iFOBT missed one third of the cancers, only one specimen was collected at a single point in time. Both collection of more than one specimen and programmatic (ie, sequential) testing would very likely improve sensitivity

with a small, if any, decline in specificity. The overall test characteristics for iFOBT are better than those for gFOBT as determined from other studies. However, this study did not directly compare gFOBT and iFOBT, so the true difference in test characteristics cannot be properly determined.

Subsequent work by Guittet et al compared the performance of gFOBT and iFOBT among 10,673 average-risk persons aged 50–74 years.[61] As opposed to the study by Morikawa et al,[43] in which colonoscopy was performed irrespective of iFOBT results, subjects were offered colonoscopy only if either FOBT was positive. Therefore, this study[61] could provide information on relative, not absolute, test characteristics. gFOBT was collected in the usual fashion; iFOBT collection (Immudia/RHPA; Fujirebio) required 2 samples obtained on 2 different days and used an automated reading process (Magstream 1000; Fujirebio). The threshold for a positive iFOBT was varied from the usual value of 20 ng/mL up to 75 ng/mL. Of 886 (8.3%) persons with at least one positive FOBT, 711 (80%) underwent colonoscopy, with results available for 644 persons (91%), of whom 21 had cancer and 149 had high-risk adenomas. At the 20-ng/mL threshold, iFOBT detected 1.5 times as many cancers and nearly 2.6 times as many high-risk adenomas; however, it also increased the relative false-positive rates. The number of false-positive results associated with the detection of one extra advanced neoplasm (cancer or adenomas ≥10 mm or high-grade dysplasia) was 2.17. At a threshold of 50 ng/mL, iFOBT detected 2.33 times as much advanced neoplasia without a decrement in specificity (false-positive ratio of 0.99). At 75 ng/mL, iFOBT detected 90% more advanced neoplasms with a 33% decrease in the false-positive risk.

This study shows that iFOBT has better relative test characteristics than gFOBT and provides a greater advantage for detection of advanced adenomas than for cancer. It also nicely demonstrates the trade-off involved in varying the threshold for a positive test. A low threshold detected more advanced neoplasia (and relatively more advanced adenomas than cancers) but was associated with more false-positive tests: the ratio of false-positive to true-positive tests was 47.4 for cancer and 2.17 for advanced neoplasia. Increasing the threshold lowers the relative sensitivity for both cancer and advanced adenomas but reduced the number of false-positive tests. This study supports the superior performance of iFOBT and suggests that the gain in sensitivity will be important for enhancing the detection of advanced adenomas more so than for cancers. It also demonstrates the ability to vary the test threshold to optimize the balance between sensitivity and specificity.

In another study involving quantitative iFOBT,[62] Levi et al evaluated 1000 ambulatory subjects who either had symptoms or a history of adenomatous polyps and who were scheduled for an elective colonoscopy. Each subject provided 3 iFOBT samples, the highest value of which was compared with colonoscopy findings. Specimens were processed by the OC-MICRO instrument (Eiken Chemical Co., Tokyo, Japan). The threshold for a positive test was varied from 50 to 150 ng/mL in 25 ng/mL increments. Ninety-one subjects had clinically significant neoplasia: 17 had cancer (of which 16 were early stage), and 74 had advanced adenomas. Mean fecal hemoglobin level increased with nonoverlapping confidence limits as the most advanced finding proceeded from normal colon to nonadvanced adenoma to advanced adenoma to cancer. At the usual threshold of 100 ng/mL, test sensitivity and specificity for cancer were 88% and 90%, respectively, whereas those for advanced neoplasia were 62% and 93%, respectively. Lowering the threshold to 75 ng/mL increased sensitivity for cancer to 94% and to 67% for advanced neoplasia; however, it also slightly reduced specificity. Cancer sensitivity was 100% when 3 samples were used at a threshold of 50 ng/mL, although at the cost of a specificity of 84%.

Although this was not an asymptomatic, average-risk study population, the early and curable spectrum of disease and disease prevalence comparable with the screening setting make the findings generalizable to the screening setting. This study,[62] as well as the previous one,[61] suggests the potential for quantitative iFOBT, where the threshold may be adjusted to fit the clinical and/or economic setting. The study by Levi et al,[62] in addition, may be used to communicate patient-specific information about risk for advanced neoplasia, where the risks for cancer and advanced neoplasia can be quantified for patients.

Two other studies suggest that the performance of iFOBT is better than high-sensitivity gFOBT because of the latter's lower specificity.[63,64] Wong et al compared Hemoccult SENSA (HOS) with FlexSure OBT in 135 consecutive patients who were referred for colonoscopy. All patients submitted 3 samples for each test without dietary restriction. The sensitivity, specificity, and positive predictive value for significant colorectal neoplasia (adenomas ≥ 1.0 cm and cancer) were 91% (6 of 7), 70%, and 18%, respectively, for Hemoccult SENSA, and were 82% (5 of 7), 94%, and 47% for FlexSure OBT.[64] A similar study, by Levi et al, compared HOS with OC-MICRO, an iFOBT in 151 patients referred for colonoscopy either because of a positive HOS or because they were above average-risk. Patients prepared 3 cards for both FOBTs and were asked to follow instructions about diet and medications before and during preparing the specimens. Sensitivity, specificity, and positive predictive value for significant colorectal neoplasia were 75%, 34%, and 12%, respectively, for HOS, and were 75%, 94%, and 60% for OC-MICRO.[63] For a positive gFOBT, 4 times more colonoscopies were needed to identify a significant neoplasm as compared with iFOBT and at more than 4 times greater costs. Although the number of patients in these 2

studies is small, the low specificity of the high-sensitivity gFOBT suggests that it is less efficient for screening than iFOBT. The new CRC screening and surveillance guidelines recommend either annual gFOBT with high sensitivity for cancer or annual iFOBT with high sensitivity for cancer.[65] In our opinion, the studies discussed here suggest that iFOBT is superior to gFOBT and should replace gFOBT wherever FOBT is a component of a recommended screening strategy. Although high-sensitivity gFOBT will detect more clinically significant neoplasia than gFOBT (ie, Hemoccult II), the lower specificity will make a gFOBT screening strategy more costly than will an iFOBT strategy. iFOBT should be included in CRC screening models of cost-effectiveness to determine factors such as optimal test threshold (for the quantitative version), screening interval, and number of samples required.

Blood-Based Assays

Perhaps the ultimate test for CRC screening—the Holy Grail—is a blood test that identifies people who have either current advanced neoplasia or increased lifetime risk for it. A myriad of studies has attempted to identify such a test, although no reliable serum biomarkers for advanced colorectal neoplasia have heretofore been described. Most of these studies have involved proteomics, which is the study of protein expression in biologic samples. Using proteomics for cancer detection involves identifying biomarkers—either individual proteins or proteomic patterns (also known as "expression signatures")—that discriminate between persons with and without cancer or advanced colorectal neoplasia. As with the literature on fecal DNA, most of the studies involving serum biomarkers are case-control studies, which usually do not sample the entire spectrum of diseased or nondiseased subjects. Furthermore, case-control studies are prone to bias and chance and, particularly when the number of candidate markers exceeds the number of study subjects, require independent validation in a separate sample of subjects. Two recent studies depict the current status of this area.

Habermann et al[66] used surface-enhanced laser desorption/ionization time-of-flight mass spectrometry and enzyme-linked immunosorbent assay techniques to identify proteins with differential expression in the sera of 58 patients with CRC (19 of whom were early stage) and 32 healthy controls.[66] Candidate markers were subject to validation in an independent sample of 38 patients with CRC (9 early stage) and 21 controls. In addition, there were 36 other patients who had polyps of various types.

The marker with the greatest difference in expression between cases and controls was a member of the complement system, the stable form of C3a anaphylotoxin. Based on thresholds derived from both sets of specimens, C3a anaphylotoxin had a sensitivity of 92%–97% for cancer, a sensitivity of 92%–94% for polyps, and a specificity of 90%–96%. Several specimens from both sets had indeterminate values and were not included in analysis.

Despite the apparent promise of this study,[66] it has several limitations. First, the spectrum of cancer cases included several with advanced disease, which limits the clinical utility of any screening test. Second, the spectrum of controls was limited to young, healthy subjects, and not all polyps were adenomas; these limitations has the potential to overestimate specificity. Third, both sets of specimens were used to determine thresholds for assessing test characteristics. As a result, further independent validation of these threshold values is required. Finally, C3a anaphylotoxin is overexpressed in breast cancer and, therefore, may not be neoplasm specific.

A more recent study examined the test characteristics of 2 nuclear structural proteins: colon cancer-specific antigen (CCSA)-3 and CCSA-4.[67] This study was based on previous work showing that changes in nuclear matrix proteins may be a signature of (ie, highly specific for) cancer cells. Such alterations in nuclear matrix proteins have been identified in other cancers, including breast, prostate, and bladder.[68] More topic-specific previous studies have identified CCSAs 2-5 from colorectal neoplasia by 2-dimensional gel electrophoresis; CCSA-3 and CCSA-4 were found to be expressed early. Using thresholds established from previous samples, the investigators collected serum preoperatively and prior to colonoscopy in 28 persons with CRC, 30 with a normal colonoscopy, 23 with only hyperplastic polyps, 36 with nonadvanced adenoma, 18 with advanced adenoma, and 125 with benign disease or other types of cancer.

At a cutoff of 2 μg/mL for CCSA-3 and 3 μg/mL for CCSA-4, both markers had a cancer sensitivity of 100%. For the combined end point of cancer and advanced adenomatous polyps, sensitivity for CCSA-3 was 89.1%, and sensitivity for CCSA-4 was 84.8%. For either marker being positive, sensitivity was 91.3%. Specificity values in subjects with normal colons, hyperplastic polyps, or nonadvanced adenomas were 82.0% for CCSA-3, 91.0% for CCSA-4, and 78.7% for the combination. Discrimination, as measured by receiver operating characteristics curve analysis, was 0.94 for both markers, indicating excellent discrimination. Although these results suggest that CCSA-3 and CCSA-4 show potential for serum markers of advanced neoplasia, further study is required, including assessing test characteristics in an unselected asymptomatic population and determining the protein sequence and identification of the genes that encode these proteins.

There are numerous methodologic challenges to molecular marker research that have been well described.[69] In general, successful biomarker discovery requires a well-characterized study population with appropriate spectra of cases and controls; high-quality samples that are acquired and processed in a uniform fashion; a reliable analytic mass spectrometry platform; and independent

validation, preferably by independent groups of investigators. Future biomarker researchers and consumers of this body of literature will have to consider carefully these requirements when designing and evaluating subsequent studies.

Computed Tomographic Colonography

Patients who have undergone computed tomographic colonography (CTC) and colonoscopy on the same day often prefer the experience of CTC[70–76] and clearly prefer the experience of CTC over that of double contrast barium enema.[74] American studies have remained focused on CTC with thorough bowel preparation,[73,74,77,78] although surveys indicate that bowel preparation is the single largest deterrent to adherence with CRC screening.[79–81] No major step toward CTC without preparation has been made in the United States. To our knowledge, evidence that CTC would improve adherence to screening is yet to be published.[82]

The performance characteristics of CTC are superior to that of double contrast barium enema.[74] Meta-analysis found that the overall sensitivity of CTC for large polyps was 85% (range, 48%–100%) when compared with the reference standard, which was conventional colonoscopy, optimized colonoscopy (videotape review), or colonoscopy with CTC-assisted segmental unblinding.[83] One[73] of 3[73,74,77] major US multicenter trials obtained results for CTC comparable with colonoscopy, and some believe that methodologic differences between the performance of CT colonography in this trial and others account for the wide discrepancies in results.

A nonrandomized single center trial compared the yield of CTC with conventional colonoscopy in 6283 patients.[78] Among 3120 patients in the primary CTC group, 246 (7.9%) were referred for colonoscopy. There were 2434 polyps resected in the primary conventional colonoscopy, compared with 561 in the primary CTC arm. There were more perforations in the conventional colonoscopy arm (7 vs 0, respectively), but there was no difference in the prevalence of advanced adenomas (3.2% with primary CTC vs 3.4% with primary colonoscopy) between the study arms. The results appeared to heavily favor CTC, but there was an unexplained higher prevalence of cancer and flat adenomas in the CTC arm (suggesting 2 distinct study populations) as well as a higher than expected perforation rate in the conventional colonoscopy arm (1 in 452 colonoscopies). The overall adenoma detection rate in the colonoscopy arm was not reported, preventing assessment of the quality of mucosal inspection during colonoscopy.

At this writing, the results of the US multicenter trial (The American College of Radiology Imaging Network trial) are still unpublished. A preliminary announcement of the principle findings reported a sensitivity of 90% for polyps $\geq$1 cm in size, with a specificity of 86% for polyps $\geq$1 cm in size and positive predictive values of approximately 25% for all sizes of polyps.[84] These results indicate that the sensitivity for large polyps is acceptable for CTC and almost certainly much better than double contrast barium enema.[85] The specificity and positive predictive value in this trial are considerably lower than that achieved in the studies in which CTC performed the best.[73,83]

Several studies have reported that nonradiologists can read CTC studies as accurately as radiologists.[86] The American Gastroenterological Association published guidelines on training and performance of CTC by gastroenterologists.[87]

Controversy prevails regarding the reporting and management recommendations for polyps $<$1 cm in size, visualized on CTC studies. The American College of Radiology recommended that polyps $\leq$5 mm on CTC studies not be reported and that patients with 1 or 2 polyps 6–9 mm in size can be offered "CTC surveillance" as an alternative to prompt colonoscopy and polypectomy.[88] The CTC surveillance consists of a repeat CTC in 3 years. The American College of Gastroenterology[89] and American Gastroenterological Association[87] both recommended that patients with any polyp $\geq$6 mm in size and patients with 3 or more polyps $\leq$5 mm in size read with high confidence be referred for colonoscopy and polypectomy.

The policy of CTC surveillance for 6- to 9-mm polyps has been called the "watch and wait" policy. A decision analysis utilized a Markov model to compare the "watch and wait" strategy to prompt colonoscopy and polypectomy for 6- to 9-mm polyps detected at CTC.[90] The prompt polypectomy strategy resulted in 14 total deaths and 39 incident cancers per 100,000 patients, compared with 79 total deaths and 773 incident cancers with the "watch and wait" policy. Sensitivity analyses found that the results were robust except at extreme parameter values. However, a decision analysis performed by radiologists supported the "watch and wait" strategy.[91]

Two large studies from outside the United States found a higher risk of perforation (1 in 1313 and 1 in 1696, respectively) from CTC than anticipated.[92,93] However, not all perforations were symptomatic, and most occurred in patients with symptoms or hernias.[92,93] The risk of perforation from CTC in screening patients is probably lower than for conventional colonoscopy in many settings.

The radiation risk associated with CTC is also controversial. Radiation risks have recently received increased attention with regard to the risk of lung and breast cancer after coronary angiography scanning[94] and with solid tumor development after CT scanning in general.[95] However, an analysis from the Health Physics Society concluded that the health risks of low-dose exposures below 5–10 mrem (which includes a single CTC study) are "either too small to be observed or are nonexistent."[96] On the other hand, a white paper from the American

College of Radiology made recommendations to numerous parties regarding radiation risk reduction, stating that "the current annual collective dose from medical exposure in the United States has been calculated as roughly equivalent to the total worldwide collective dose generated by the [nuclear] disaster at Chernobyl . . . and . . . may likely result in an increase in the incidence of imaging-related cancer in the US population in the not-too-distant future."[97] In an analysis specific to CTC, Brenner and Georgsson used a linear nonthreshold model to estimate the risk of solid tumor development from a single CTC at age 50 years at 1 in 714.[98] However, the authors acknowledged that their methods may not apply to low-dose exposures. Others have argued that any risk of cancer induced by radiation in this range associated with radiation in asymptomatic people is comparable with the risk of perforation from colonoscopy and, therefore, warrants discussion with patients.[88]

Current procedural terminology may receive a category 1 CPT code for screening in early 2010. As its use for screening develops, it will be important to monitor its impact on relevant outcomes, including adherence to CRC screening, complications of colonoscopy, polypectomy rates, and prevention of CRC, and whether detection of extracolonic findings has a positive risk-to-benefit ratio.

Postpolypectomy Surveillance

In 2006, the Multisociety Task Force on Colorectal Cancer and the American Cancer Society issued joint recommendations for postpolypectomy surveillance.[99] The 2 groups had previously issued separate and differing guidelines,[100,101] and merging recommendations was done partly to improve adherence by physicians through uniformity in guideline presentation. Increased emphasis is placed on high-quality baseline clearing examinations and expanded intervals in low-risk patients with adenomas. Polyp and patient characteristics at baseline colonoscopy have been identified in a number of studies and were considered to potentially stratify patients according to their risk of an advanced adenoma at a subsequent colonoscopy. Factors considered to be consistently or frequently represented across studies as predictors of advanced adenomas were ≥3 adenomas vs 1 or 2, greater than 25% villous elements in any adenoma, any adenoma with high-grade dysplasia, and any adenoma ≥1 cm in size.[99] A report of patients in the VA Cooperative Screening Colonoscopy Study and followed up after 5 years confirmed each of these factors as predictors of advanced adenomas.[102] Factors identified in the literature review as predictors of advanced adenomas but not yet included as risk stratifiers in the guidelines include increasing age, a family history of CRC in a parent, and proximal colon location of baseline adenomas.[99]

Serrated polyps, including hyperplastic polyps, sessile serrated polyps (or sessile serrated adenomas), and serrated adenomas, are considered of increasing importance. Hyperplastic polyps may become serrated adenomas, particularly in the proximal colon and in older women.[103,104] This process involves gene promoter hypermethylation, particularly of the hMLH1 gene; BRAF mutations; and, frequently, microsatellite instability. Current opinion is that small hyperplastic polyps in the distal colon are less likely to bear worrisome molecular profiles, whereas larger serrated lesions in the proximal colon are of greater importance. In a colonoscopic study, sessile serrated adenomas constituted 9% of all polyps and 22% of all serrated polyps.[104] Serrated polyps may be endoscopically subtle because they are typically pale, have less distinct edges compared with adenomas, and may be covered with mucus.[105] Serrated polyps in the proximal colon should be carefully searched for and fully resected during colonoscopy.

The Multisociety Task Force/American Cancer Society panel concluded that there was insufficient evidence to structure recommendations for surveillance intervals after resection of serrated lesions, other than small distal colon hyperplastic polyps.[99] It is probably reasonable to treat serrated adenomas and sessile serrated polyps as adenomas with regard to surveillance.[99] Patients with resected large or numerous hyperplastic polyps in the proximal colon should have their intervals between examinations shortened, although to what extent is unclear.

The World Health Organization established criteria for a hyperplastic polyposis syndrome, including 30 or more hyperplastic polyps anywhere in the colon, ≥5 hyperplastic polyps proximal to the sigmoid-descending colon junction, or hyperplastic polyp in the proximal colon in a patient with family history of hyperplastic polyposis.[106] Patients with the syndrome appear to be at increased risk of CRC, but the optimal management and surveillance of these patients remain uncertain, as is any genetic basis for the syndrome.[107]

Recent surveys report that some gastroenterologists and many general surgeons perform colonoscopy at intervals that are shorter than are currently recommended in any guideline.[108] When asked about various polyp scenarios, primary care physicians also frequently recommended colonoscopy at shorter intervals between examinations than those in guidelines.[109] The reasons why some physicians do not follow the guidelines, and for variation between specialties, remain unclear.

Post-CRC Resection Surveillance

The fundamental aim of surveillance after CRC resection is to detect tumor recurrence and metachronous neoplasms at an early stage to allow curative re-resection, or at least reasonable palliation. In clinical practice, a wide array of modalities is used in conjunction

with clinical assessment by history and physical examination.[110] Certain tests such as complete blood counts, liver tests, fecal occult blood tests, and chest x-ray are not routinely recommended for surveillance in the absence of symptoms.[111,112] However, laboratory tests such as carcinoembryonic antigen and endoscopy are an integral part of surveillance. To date, 8 randomized controlled trials have assessed the effectiveness of surveillance strategies after curative resection for CRC,[113–120] and these studies have recently been analyzed in a Cochrane systematic review.[121] Meta-analysis of 6 of the trials[113–118] showed significantly improved 5-year survival for the intensive follow-up strategy (OR, 0.73; 95% CI: 0.59–0.91). The mean difference for time to recurrence was reduced by the intensive approach (OR, −6.75 months; 95% CI: −11.06 to −2.44), and the performance of more tests was associated with a reduction in mortality (OR, 0.64; 95% CI: 0.49–0.85). Additionally, liver imaging (vs no liver imaging) was associated with mortality reduction (OR, 0.64, 95% CI: 0.49–0.85), in contrast to carcinoembryonic antigen measurement (OR, 0.57; 95% CI: 0.26–1.29). These findings show that there is a survival benefit to intensive surveillance after curative CRC resection; however, the wide variation in follow-up strategies does not allow definitive conclusions about the optimal combination and frequency of tests.

Generally, patients with stage I, II, or III, and selected patients with stage IV CRC, are candidates for postoperative surveillance colonoscopy.[122] Patients with CRC may harbor synchronous cancers and precancerous polyps, mandating complete colonoscopic clearing (visualization and resection of polyps) at the time of the diagnosis of the index primary tumor. After surgery, patients remain at increased lifelong risk for developing recurrent colonic neoplasms (local recurrences, second primary tumors, and adenomatous polyps); thus, colonoscopy is a key component of follow-up. Colonoscopy is generally not recommended for the purpose of detection of intraluminal anastomotic recurrences because of low yield outside the rectum (estimated to range from 2% to 4%) and because most anastomotic recurrences are usually heralded by symptoms and are accompanied by locally advanced or metastatic disease making curative re-resection possible in only a minority of patients.[122] Rather, the main roles of colonoscopy after CRC resection are the detection of metachronous CRCs at a curable stage and the detection and removal of precursor adenomatous polyps. In the past, clinical practice guidelines generally recommended surveillance colonoscopy 3 and 5 years after surgery based on extrapolations from the National Polyp Study.[101,111,112,123] However, recent studies have shown an alarmingly elevated incidence of "early metachronous" CRCs, or cancers that are detected within the first few years after surgery, despite apparently thorough perioperative clearing.[124] These observations have led the United States Multisociety Task Force on Colorectal Cancer and the American Cancer Society to develop unified guidelines in 2006 recommending a colonoscopy at 1 year after surgery (or after the perioperative clearing colonoscopy), in addition to high-quality perioperative clearing to exclude synchronous neoplasia.[122] Studies published subsequent to the updated guidelines have provided additional support for follow-up colonoscopy 1 year after resection. In a study conducted within a large health maintenance organization in Washington State, 1002 patients who had undergone curative resection for CRC were evaluated for surveillance colonoscopy findings and survival.[125] Twenty patients (3.1%) were diagnosed with a second primary CRC, including 9 cancers that were detected within 18 months of the initial cancer diagnosis. Additionally, patients who underwent colonoscopy within 18 months were less likely to have advanced neoplasia on subsequent surveillance than patients whose follow-up occurred between 30 and 60 months after surgery (6.9% vs 15.5%, respectively, $P = .02$).[125] The 5-year follow-up findings of VA Cooperative Study No. 380 were comparable:[102] In this prospective study, 3121 asymptomatic subjects ages 50–75 years underwent screening colonoscopy in the Department of Veterans Affairs between 1994 and 1997. Cohorts were defined according to baseline findings with neoplasia-free patients serving as controls, and relative risks for advanced neoplasia within 5.5 years were calculated. The relative risk (RR) in patients with baseline adenoma with high-grade dysplasia was 6.87 (95% CI: 2.61–18.07, $P < .001$) and 13.56 (95% CI: 5.54–33.18, $P < .001$) in patients with baseline cancer. Fifteen of 21 (71%) interval cancers or adenomas with high-grade dysplasia were found in the first 36 months after baseline colonoscopy, and 4 were discovered within 12 months. Five cancers recurred in patients who had CRC at baseline, and 4 of 5 were detected within 18 months.[102]

Quality Issues in the Performance of Colonoscopy

Widely held assumptions that colonoscopy and polypectomy prevent nearly all CRCs, based largely on the National Polyp Study[126] but supported by several other studies,[127–130] have been recently challenged. A population-based study of 35,975 symptomatic patients who had a negative colonoscopy in Manitoba in the 1990s demonstrated that, for each of the first 5 years after the negative colonoscopy, the protection against CRC incidence was less than 50%.[131] Similarly, adenoma cohorts followed after clearing colonoscopy in a fashion similar to the National Polyp Study have demonstrated substantially lower levels of protection than observed in the National Polyp Study.[132–134] In particular, 3 chemoprevention trials in which patients had undergone clearing colonoscopy incurred a rate of 1.74 cancers per 1000 patient-years of observation, approximately 3 times that of the National Polyp Study. No protective effect against

CRC was observed because the cancer incidence was no different than expected based on Surveillance Epidemiology and End Results program (standardized incidence ratio, 0.98; 95% CI: 0.63–1.54).[133]

Indirect evidence suggests that suboptimal quality of mucosal inspection by some examiners is an important contributor to failures of colonoscopy to prevent CRC. Barclay et al[135] performed a prospective study of 2000 screening colonoscopies performed by 12 experienced colonoscopists in private practice working in an open access ambulatory surgery center. The range of adenoma detection per colonoscopy extended from 1.05 to 0.1. There was a strong correlation with increased adenoma detection and longer withdrawal time. Among endoscopists with a mean withdrawal time greater than 6 minutes, the prevalence of adenomas ≥1 cm in size was 6.4% vs 2.6% in colonoscopies performed by endoscopists with average withdrawal time in normal colonoscopies less than 6 minutes ($P = .005$).[135] A study of 9 endoscopists at a university hospital identified a range of prevalence of adenomas detected in persons age 50 years and older of 40% to 16%.[136] The highest level adenoma detector detected 11 times more patients with 3 or more adenomas and 3 times more patients with adenomas ≥1 cm in size compared with the lowest level adenoma detector. In both studies,[135,136] there was a strong correlation between overall adenoma detection and detection of large adenomas. A single center study of 43 endoscopists performing 10,955 colonoscopies found that polyp detection was strongly correlated with withdrawal time ($r = 0.76$; $P < .0001$) and that a median level of polyp detection occurred at a withdrawal time of 6.7 minutes. These studies support recommendations initially made by the US Multisociety Task Force in 2002,[137] and subsequently by a joint task force of the American College of Gastroenterology/American Society for Gastrointestinal Endoscopy in 2006,[138] that individual endoscopists should measure their adenoma detection rates in patients undergoing screening colonoscopy who are age 50 years and older and that adenomas should be detected in at least 25% of men and 15% of women. As a secondary measure of the quality of mucosal inspection, the average time spent examining the colon in normal colons in which no biopsies or polypectomies were performed should average at least 6 minutes.[138] The optimal time for withdrawal has not yet been determined, but these studies[135,136,139] support the current recommendation of at least 6 minutes.

Bowel preparation has also emerged as an important contributor to failed detection of both small polyps[140] and large polyps.[140,141] Prospective studies have identified bowel preparation as a predictor of adenoma prevalence[142] and that, for both polyethylene glycol-based preparations and sodium phosphate-based preparations, the administration of half of the preparation on the day of the colonoscopy (often called "split" dosing) substantially improves the quality of preparation, particularly in the right colon.[142–144]

Two recent studies have suggested that ineffective polypectomy contributes to 27%–31% of interval colon cancers, although the methodology cannot differentiate ineffective polypectomy from missed lesions with confidence.[145,146] Unfortunately, prospective studies demonstrating optimal polypectomy technique to achieve a balance of effective resection and safety have not been performed.

Performance of colonoscopy by primary care physicians and in office practice was shown to predict an increased risk of interval cancers in a study from Ontario.[147] An earlier study also found that performance of colonoscopy by primary care physicians was a risk factor for development of interval cancers.[148] These results emphasize the need for adequate training of colonoscopists and incorporation of continuous quality improvement programs into colonoscopy delivery by all specialties.

The single greatest downside of colonoscopy as a screening test is perforation. Perforation rates have been reported to range from 1 in 450 in a single center screening study[78] to an estimate of 1 in 1000 overall in the United States for screening colonoscopies in the Medicare population,[149] 1 in 1000 in a large health maintenance organization in the United States,[150] to 1 in 10,000 in screening colonoscopy in Poland.[151] Quality guidelines have recommended that perforation rates should be less than 1 in 500 overall and less than 1 in 2000 in screening populations.

CRC Screening and Surveillance in Special Populations

Family History of CRC

FDRs of patients with CRC are at higher risk of developing CRC and are advised to undergo screening colonoscopy at an earlier age and/or more frequently than average-risk patients. The data regarding FDRs of patients with adenomas have been less consistent. In particular, it was unclear whether and to what extent family history of a large or advanced adenoma affected risk of CRC. The risk of developing colorectal neoplasia among FDRs of individuals with large adenomas was recently quantified in a case-control study conducted in France.[152] A colonoscopy was offered to FDRs of 306 index cases with adenomas ≥10 mm, and 168 were enrolled; underwent colonoscopy; and were matched for age, sex, and geographical area with 2 controls (n = 307) who had no family history of CRC or adenomas and who had undergone colonoscopy for minor symptoms. The prevalence of large adenomas and cancers was 8.4% and 4.2%, in relatives and controls, respectively. ORs associated with a history of large adenomas in relatives were 2.27 (95% CI: 1.01–5.09) for cancers or large adenomas, 1.21 (95% CI: 0.68–2.15) for small adenomas, and 1.56 (95% CI: 0.96–2.53) for all colorectal neoplasia. The risk

of large adenomas and cancers was higher in relatives of index cases younger than 60 years (OR, 3.82; 95% CI: 0.92–15.87) and when the index case had large distal adenomas (OR, 3.14; 95% CI: 1.27–7.73). Despite the small sample size, this study suggests that FDRs of patients with large adenomas have a 2-fold increased risk of CRC and large adenomas and should be specifically targeted for screening colonoscopy.[153] An important unanswered question is whether this applies to FDRs of patients with 1 or 2 small (<10 mm) adenomas. Current guidelines recommend screening FDRs of patients with adenomas of any size with the same intensity as FDRs of patients with CRC;[101] however, this study suggests that this approach may be unnecessarily aggressive. The principle of risk stratification applied for screening and postpolypectomy surveillance can and should be extended to screening of FDRs of patients with adenomas, but awaits further well-conducted studies, especially in patients with small adenomas.

Hereditary Nonpolyposis CRC

Hereditary nonpolyposis CRC (HNPCC; also known as Lynch syndrome) accounts for 2%–3% of all cases of CRC in the United States and is due to germ-line mutations in mismatch repair (MMR) genes such as MSH2, MSH6, MLH1, and PMS2.[154,155] Current screening strategies rely on the identification of at-risk patients via clinical criteria (Amsterdam I and II, Bethesda and revised Bethesda criteria) and testing for microsatellite instability (MSI) with germ-line testing in patients with MSI-high tumors.[156] Recent studies have shown that this approach may be inadequate because it misses a significant proportion of patients with Lynch syndrome who do not meet clinical criteria. Hampel et al screened 1066 patients with CRC for MSI and searched for germ-line mutations in the MLH1, MSH2, MSH6, and PMS2 genes in patients with positive MSI.[155] They found 208 patients with MSI, 23 of whom had a mutation in one of the MMR genes (2.2%). Ten of 23 patients were older than 50 years, and 5 met neither the Amsterdam nor the Bethesda guidelines for the diagnosis of HNPCC. Testing of family members of the patients with MMR gene mutations yielded an additional 52 persons with HNPCC mutations.[155] Although this study shows that the Amsterdam and Bethesda guidelines may miss a significant proportion of patients with HNPCC, we are still not at a point where molecular screening of all sporadic CRCs can be advocated because there are still important cost-effectiveness, practical and logistical, and ethical issues that need to be addressed. Additionally, the Amsterdam and Bethesda guidelines remain important to identify high-risk patients, even in instances in which no MMR mutation is identified. For example, patients who meet Amsterdam I criteria but have no evidence of MMR mutations have been shown to have a lower risk of CRC than patients who meet the criteria and have an MMR mutation,[157] and patients with an autosomal dominant family history of CRC but no MSI do not require colonoscopic surveillance with the same intensity as patients with HNPCC.[158] "Familial CRC type X" has been proposed to describe instances in which there is familial aggregation of CRC cases sufficient to meet Amsterdam criteria but no molecular evidence of HNPCC.[157]

Chemoprevention of CRC

The considerable morbidity and mortality attributable to CRC, and the relatively low rates of screening in the United States, have led to the development of ancillary preventive strategies such as chemoprevention. In principle, chemoprevention aims to protect against the development of CRC by interfering with the progression of adenomas to invasive cancers. Definitive chemoprevention trials that use CRC incidence or mortality as the primary outcome have not been conducted and are unlikely to be conducted because of the large sample size and long follow-up; thus, most studies have used adenoma development as a surrogate outcome. Several agents have been studied in various settings, including primary prevention in average-risk individuals, and secondary prevention after resection of adenomas, and after curative therapy for CRC.[159] Among all chemopreventive agents, aspirin and calcium appear to be the front-runners; however, no chemopreventive agent is a substitute for adequate screening and surveillance.

Aspirin and Nonaspirin Nonsteroidal Antiinflammatory Drugs

The mechanism by which aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) interfere with the development of adenomas and CRC is not well understood. Its effect is partly mediated by the inhibition of cyclooxygenase-2 (COX-2), an enzyme that is overexpressed in nearly 90% of CRCs.[160] Sulindac[161] and celecoxib[162] have been shown in randomized trials to decrease the adenoma burden in patients with familial adenomatous polyposis; however, this does not replace prophylactic colectomy as the standard of care for familial adenomatous polyposis nor is the requirement for frequent endoscopic surveillance diminished. Evidence for the efficacy of NSAIDs in familial adenomatous polyposis has spurred studies in patients without genetic syndromes. Two trials published in 2003 showed that aspirin reduces the risk of recurrent adenomas in patients with a history of CRC or adenomas.[163,164] In one study, 1121 patients with a history of adenomas were randomized to aspirin 81 mg daily, aspirin 325 mg daily, or placebo, and follow-up colonoscopy was performed at least 1 year after randomization. The incidence of one or more adenomas was 47% in the placebo group, 38% in the 81-mg group, and 45% in the 325-mg group ($P = .04$).[163] In the study by Sandler et al,[164] 517 patients with a history of CRC were randomized to aspirin 325 mg daily

or placebo and underwent at least one colonoscopy examination after a median of 13 months. One or more adenomas were found in 17% of patients in the aspirin group and 27% of patients in the placebo group (P = .004), leading to early termination of the trial. The adjusted RR of any recurrent adenoma in the aspirin group, as compared with the placebo group, was 0.65 (95% CI: 0.46–0.91). The time to the detection of a first adenoma was longer in the aspirin group than in the placebo group (indicating that aspirin delayed the development of adenomas); however, the mean size of adenomas and the proportion of patients with advanced adenomas were not significantly different between the 2 groups.[164] Although these 2 trials provided proof of concept that aspirin can reduce the risk of recurrent adenomas in the short-term, important questions remained regarding dose, duration of use, long-term effects, ability to prevent CRC, and whether aspirin should be used for primary chemoprevention in average-risk situations.

Considerable light was shed on these issues with the recent publication of an update to the Nurses' Health Study.[165] In this prospective cohort of 82,911 women who provided data on medication use biennially since 1980 and followed up until 2000, 962 cases of CRC were documented. Among women who regularly used aspirin (≥2 [325 mg] tablets per week), the adjusted RR for CRC was 0.77 (95% CI: 0.67–0.88) compared with nonregular users. Significant risk reduction was not observed until more than 10 years of use ($P \leq .001$ for trend). The benefit appeared related to dose: compared with women who reported no use, the adjusted RRs for cancer were 1.10 (95% CI: 0.92–1.31) for women who used 0.5 to 1.5 325-mg aspirin tablets per week, 0.89 (95% CI: 0.73–1.10) for 2 to 5 aspirin per week, 0.78 (95% CI: 0.62–0.97) for 6 to 14 aspirin per week, and 0.68 (95% CI: 0.49–0.95) for more than 14 aspirin per week ($P < .001$ for trend). Women who used more than 14 aspirin per week for longer than 10 years had an adjusted RR for cancer of 0.47 (95% CI: 0.31–0.71). A similar dose-response relationship was found for nonaspirin NSAIDs ($P = .007$ for trend). The incidence of reported major gastrointestinal bleeding events was also dose related.[165] In contrast, the Women's Health Study found no reduction in risk of CRC after an average of 10 years of aspirin use; however, the dose used was low (100 mg every other day).[166]

The recently published results of a secondary analysis of the British Doctors Aspirin Trial and UK-TIA trial provide additional evidence that the chemopreventive effect of aspirin depends largely on dose and duration of use;[167] in this study, aspirin reduced the incidence of CRC (hazard ratio [HR] 0.74, 95% CI: 0.56–0.97, $P = .02$); however, this effect was only seen after a latency of 10 years (years 0–9, HR, 0.92; 95% CI: 0.56-1.49; $P = .73$; years 10–19, HR, 0.60; 95% CI: 0.42–0.87; $P = .007$), was dependent on duration of scheduled trial treatment and compliance, and was greatest 10–14 years after randomization in patients who had treatment for 5 years or more (RR, 0.37; 95% CI: 0.20–0.70; $P = .002$).[167] In a separate systematic review involving 20,815 subjects in 19 case-control studies, and 1,136,110 subjects in 11 cohort studies, the same authors found that regular use of aspirin or NSAIDs was consistently associated with a reduced risk of CRC, especially after use for 10 years or more and at aspirin doses of at least 300 mg per day.[167]

The US Preventive Services Task Force recently published exhaustive systematic reviews of the literature to examine the evidence on the effectiveness and harms of aspirin and nonaspirin NSAIDs for chemoprevention of colorectal adenomas and CRC.[168,169] Regular use of aspirin reduced the incidence of colonic adenomas in randomized controlled trials (RR, 0.82; 95% CI: 0.7–0.95), case-control studies (RR, 0.87; 95% CI: 0.77–0.98), and cohort studies (RR, 0.72; 95% CI: 0.61–0.85). In cohort studies, regular use of aspirin was associated with RR reductions of 22% for CRC incidence. The benefits from chemoprevention were more evident when aspirin was used at a high dose and for periods longer than 10 years; however, aspirin use was associated with a dose-related increase in incidence of gastrointestinal complications.[168] The data regarding nonaspirin NSAIDs were comparable:[169] CRC incidence was reduced with nonaspirin NSAIDs in cohort studies (RR, 0.61; 95% CI: 0.48–0.77) and case-control studies (RR, 0.70; 95% CI: 0.63–0.78). Colorectal adenoma incidence was reduced with nonaspirin NSAID use in cohort studies (RR, 0.64; 95% CI: 0.48–0.85) and case-control studies (RR, 0.54; 95% CI: 0.4–0.74) and by COX-2 inhibitors in randomized controlled trials (RR, 0.72; 95% CI: 0.68–0.77). The ulcer complication rate associated with nonaspirin NSAIDs was 1.5% per year. COX-2 inhibitors reduce this risk but have a higher ulcer complication rate than placebo and, along with nonnaproxen NSAIDs, increase the risk for serious cardiovascular events (RR, 1.86; 95% CI: 1.33–2.59 for COX-2 inhibitors vs placebo). These findings have led the US Preventive Services Task Force to conclude that the balance of benefits to risk does not favor the use of aspirin and other NSAIDs chemoprevention in asymptomatic average-risk individuals.[170] Although aspirin and other NSAIDs may have benefit in the prevention of CRC in specific clinical settings (after CRC resection or after resection of adenomas), these agents are not a substitute for screening and surveillance, and determination of their role must take into account potential harms and whether there is an impact on the intensity of screening and surveillance.[171]

Folic Acid

It has long been thought that folate plays a protective role against colorectal neoplasia. This is based on epidemiologic evidence suggesting that low-folate diets (particularly in alcoholics) are associated with a higher risk of colorectal neoplasia, and, from the Nurses' Health

Study, which found that females consuming >400 μg per day, compared to those using <200 μg per day, had a lower risk of CRC (RR, 0.69; 95% CI: 0.54–0.93) and a lower risk of adenomas (RR, 0.66; 95% CI: 0.46–0.95).[172] The potential benefits of folate supplementation have been challenged by the findings of the Aspirin-Folate Prevention Study:[173] In this trial, 1021 subjects with a recent history of colorectal adenomas were randomized to receive 1 mg per day of folic acid or placebo and separately randomized to receive aspirin (81 mg or 325 mg per day) or placebo. Subjects underwent colonoscopy at 3 years and then at 3 to 5 years later. During the first 3 years, there was no significant difference in the incidence of colorectal adenomas (RR, 1.04; 95% CI: 0.90–1.20, $P = .58$) or advanced adenomas (RR, 1.32; 95% CI: 0.90–1.92, $P = .15$) between the folate group and the placebo group. At the second colonoscopy, the corresponding RRs were 1.13 (95% CI: 0.93–1.37, $P = .23$) and 1.67 (95% CI: 1.00–2.80, $P = .05$). Folic acid was associated with a higher risk of having 3 or more adenomas, and this persisted after adjustment for sex, age, smoking, alcohol use, BMI, baseline plasma folate, and aspirin allocation. However, subjects were enrolled in this trial at a time when folate fortification of the food supply became routine, and plasma folate levels increased (while plasma homocysteine levels decreased) over time in the placebo group, indicating that the population was relatively folate replete.[173] This "floor effect" may have altered the impact of the intervention and contributed to the null findings.

Calcium and Vitamin D

A similar issue may have contributed to the null findings of the Women's Health Initiative trial (WHI).[174] In this randomized, double-blind, placebo-controlled trial, 18,176 postmenopausal women received 1000 mg of elemental calcium and 400 IU of vitamin D3, and 18,106 received placebo for an average of 7 years. The incidence of CRC did not differ significantly between the 2 groups (HR, 1.08; 95% CI: 0.86–1.34; $P = .51$). This is in contrast to an analysis of 10 cohort studies, which reported a pooled RR for CRC of 0.78 (95% CI: 0.69–0.88; $P < .001$) for the highest vs lowest quintile of total calcium intake (combining dietary and supplemental sources).[175] There are several possible reasons for the differences between this analysis and the WHI. First, the WHI trial had 3 overlapping components (calcium and vitamin D, dietary modification, and hormone therapy), which may have resulted in confounding from cointerventions that both affected the risk for CRC and enhanced calcium absorption. Second, the participants were relatively healthy and at lower risk for CRC, such that calcium and vitamin D would have had less of a chance to demonstrate a protective effect. Third, the intervention itself—the dose and/or duration—was not adequate to detect differences in CRC incidence (in particular, the dose of vitamin D was much lower than currently recommended).[176] A recent update of the Calcium Follow-Up Study reported that the protective effect of calcium supplementation on adenoma recurrence extends for up to 5 years after cessation of active treatment.[177]

Hormone Replacement Therapy

The WHI randomized trial provided strong evidence that hormone replacement therapy (HRT) significantly reduced the risk of CRC.[178] The HR for CRC was 0.63 (95% CI: 0.43–0.92) in postmenopausal females who received estrogen and progestin compared with placebo.[178] A subsequent analysis of the WHI data showed that subjects who received estrogen alone did not experience any reduction in CRC incidence.[179] In a large case-control study based on Surveillance Epidemiology and End Results data, Newcomb et al found that use of any HRT was associated with a 20% reduction in CRC risk (95% CI: 0.6–0.9).[180] The risk reduction was observed in women who had taken estrogen plus progestin preparations (OR, 0.6; 95% CI: 0.5–0.9) but not in those on estrogen alone (OR, 0.9; 95% CI: 0.7–1.1). These findings suggest that progestin plays an important role in CRC prevention among HRT users and challenge the previously held belief that estrogen alone was responsible for this beneficial effect. Despite these findings, HRT cannot be recommended for CRC chemoprevention because of an unfavorable risk:benefit profile; the WHI was stopped in 2002 after a mean of 5 years of follow-up when the data showed an increased risk of breast cancer and cardiovascular adverse events among subjects who received HRT.[178]

Statins

There was considerable initial enthusiasm for the use of statins for chemoprevention of CRC after the publication of Poynter et al's study in 2005.[181] In this population-based, case-control study conducted in Israel, use of statins for at least 5 years was associated with a 47% RR reduction for CRC after adjustment for aspirin or other NSAID use, physical activity, hypercholesterolemia, family history of CRC, ethnic group, and level of vegetable consumption.[181] Subsequent studies have found no association between statins and CRC risk. In a case-control study involving 1809 CRC case patients and 1809 matched controls (drawn from Massachusetts hospitals and the Massachusetts Cancer Registry), regular use of statins was not associated with risk of CRC (OR, 0.92; 95% CI: 0.78–1.09), and there was no consistent trend across dose or duration of use.[182] Another large population-based, case-control study from the United Kingdom reported that prolonged use of NSAIDs and COX-2 inhibitors was associated with a reduced CRC risk, but prolonged statin use was not.[183] A recent meta-analysis of 18 studies involving more than 1.5 million patients reported no association between statin use and

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risk of CRC either among randomized controlled trials (RR, 0.95; 95% CI: 0.80–1.13; n = 6) or among cohort studies (RR, 0.96; 95% CI: 0.84–1.11; n = 3). However, statin use was associated with a modest reduction in the risk of CRC among case-control studies (RR, 0.91; 95% CI: 0.87–0.96; n = 9).[184] Thus, recent studies do not support the hypothesis that statin use is protective against CRC.

Conclusion

In this review, we have described the findings of the recent literature in the areas of primary and secondary prevention of CRC that we believe are most relevant for clinical practice. As the field moves forward, we expect further research on the refinement and diffusion of newer screening tests (CTC, fecal DNA, and iFOBT) and their effects on clinically relevant outcomes, as well as continued intense investigation for a blood-based assay for CRC/advanced neoplasia. We await further studies that quantify and attempt to improve the quality of colonoscopy and polypectomy. Perhaps central to advancing the field is the need for better risk stratification for both CRC screening and surveillance. In the short-term, risk stratification will involve deciding how to incorporate risk factors other than age and family history into decisions about when and how to screen. Although incorporating additional risk factors may make screening and surveillance more complicated, it will also make both more cost-effective and may further increase adherence.

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