

# Guidelines for Colonoscopy Surveillance After Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society

SIDNEY J. WINAWER,\* ANN G. ZAUBER,\* ROBERT H. FLETCHER,† JONATHON S. STILLMAN,\* MICHAEL J. O'BRIEN,§ BERNARD LEVIN,|| ROBERT A. SMITH,¶ DAVID A. LIEBERMAN,# RANDALL W. BURT,\*\* THEODORE R. LEVIN,†† JOHN H. BOND,§§ DURADO BROOKS,¶¶ TIM BYERS,¶¶ NEIL HYMAN,||| LYNNE KIRK,### ALAN THORSON,\*\*\* CLIFFORD SIMMANG,## DAVID JOHNSON,††† and DOUGLAS K. REX†††

\*Memorial Sloan-Kettering Cancer Center, New York, New York; †Harvard Medical School, Boston, Massachusetts; §Boston University School of Medicine, Boston, Massachusetts; ||University of Texas M.D. Anderson Cancer Center, Houston, Texas; ¶American Cancer Society, Atlanta, Georgia; #Oregon Health and Science University, Portland, Oregon; \*\*Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah; ††Kaiser Permanente Medical Center, Walnut Creek, California; §§University of Minnesota, Minneapolis, Minnesota; ¶¶University of Colorado, Denver, Colorado; |||University of Vermont, Burlington, Vermont; ###University of Texas Southwestern Medical Center, Dallas, Texas; \*\*\*Creighton University, Omaha, Nebraska; †††Eastern Virginia School of Medicine, Norfolk, Virginia; and ††††Indiana University School of Medicine, Indianapolis, Indiana

Adenomatous polyps are the most common neoplastic findings discovered in people who undergo colorectal screening or who have a diagnostic work-up for symptoms. It was common practice in the 1970s for these patients to have annual follow-up surveillance examinations to detect additional new adenomas and missed synchronous adenomas. As a result of the National Polyp Study report in 1993, which showed clearly in a randomized design that the first postpolypectomy examination could be deferred for 3 years, guidelines published by a gastrointestinal consortium in 1997 recommended that the first follow-up surveillance take place 3 years after polypectomy for most patients. In 2003 these guidelines were updated and colonoscopy was recommended as the only follow-up examination, stratification at baseline into low risk and higher risk for subsequent adenomas was suggested. The 1997 and 2003 guidelines dealt with both screening and surveillance. However, it has become increasingly clear that postpolypectomy surveillance is now a large part of endoscopic practice, draining resources from screening and diagnosis. In addition, surveys have shown that a large proportion of endoscopists are conducting surveillance examinations at shorter intervals than recommended in the guidelines. In the present report, a careful analytic approach was designed to address all evidence available in the literature to delineate predictors of advanced pathology, both cancer and advanced adenomas, so that patients can be stratified more definitely at their baseline colonoscopy into those at lower risk or increased risk for a subsequent advanced neoplasia. People at increased risk have either 3 or more adenomas, high-grade dysplasia, villous features, or an adenoma 1 cm or larger in size. It is recommended that

they have a 3-year follow-up colonoscopy. People at lower risk who have 1 or 2 small (<1 cm) tubular adenomas with no high-grade dysplasia can have a follow-up evaluation in 5–10 years, whereas people with hyperplastic polyps only should have a 10-year follow-up evaluation, as for average-risk people. There have been recent studies that have reported a significant number of missed cancers by colonoscopy. However, high-quality baseline colonoscopy with excellent patient preparation and adequate withdrawal time should minimize this and reduce clinicians concerns. These guidelines were developed jointly by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society to provide a broader consensus and thereby increase the use of the recommendations by endoscopists. The adoption of these guidelines nationally can have a dramatic impact on shifting available resources from intensive surveillance to screening. It has been shown that the first screening colonoscopy and polypectomy produces the greatest effects on reducing the incidence of colorectal cancer in patients with adenomatous polyps.

*Abbreviations used in this paper:* CI, confidence interval; FOBT, fecal occult blood testing; HNPCC, hereditary nonpolyposis colorectal cancer; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SIR, standardized incidence ratio.

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Adenomatous polyps are the most frequent neoplasm found during colorectal screening.<sup>1-4</sup> Removal of these lesions has been shown to reduce the risk for future colorectal cancer and advanced adenomas.<sup>5-12</sup> To minimize the risk for colorectal cancer further, patients with adenomas usually are placed into a surveillance program of periodic colonoscopy to remove missed synchronous and new metachronous adenomas and cancers.<sup>13-16</sup> A large number of patients with adenomas now are being discovered as a result of the increased use of colorectal cancer screening, particularly the dramatic increase in screening colonoscopy, and this places a huge burden on medical resources applied to surveillance.<sup>17-19</sup> Therefore, there is a need for increased efficiency of surveillance colonoscopy practices to decrease the cost, risk, and overuse of resources for unnecessary examinations.

Therefore, the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society have issued updated joint guidelines on postpolypectomy surveillance. These guidelines differ from the earlier guidelines in several specific ways (Table 1)<sup>13-16</sup>: we offer a consensus statement that strengthens the guidelines; we specifically examined predictors of advanced adenomas and incorporated them into the guidelines; and we emphasized the quality of baseline colonoscopy and its impact on detection of postpolypectomy colorectal cancer.<sup>5,20,21</sup> We reviewed recent evidence, particularly as it pertains to stratifying patients for future risk for advanced adenomas.

**Table 1.** Differences From Prior Postpolypectomy Guidelines

1. The overall goal of these guidelines is to identify predictors of subsequent advanced adenomas and cancers to stratify patients into lower- and higher-risk groups
2. These guidelines focus on the earlier-described risk stratification to encourage a shift from intense surveillance to surveillance based on risk; this would free up endoscopic resources for screening, diagnosis, and appropriate surveillance
3. High-quality baseline colonoscopy is emphasized as critical for effectively reducing colon cancer risk
4. Completeness of polypectomy at baseline is emphasized, particularly in the setting of piecemeal removal of large sessile polyps
5. Follow-up surveillance of hyperplastic polyps is discouraged, except in the case of hyperplastic polyposis
6. The importance of increasing awareness of hyperplastic polyposis is discussed
7. The use of FOBT during surveillance is discouraged at present, but requires further study
8. Follow-up intervals after removal of 1 or 2 small (< 1 cm) adenomas have been lengthened (5-10 years or average-risk screening options) and, within this range, left to the clinician's judgment and the patient's preference
9. Evolving technologies such as chromoendoscopy, magnification endoscopy, and computed tomography colonography (virtual colonoscopy) are not yet established as surveillance modalities

**Table 2.** Surveillance Recommendations

1. Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years; an exception is patients with a hyperplastic polyposis syndrome; they are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up evaluation
2. Patients with only 1 or 2 small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5-10 years; the precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
3. Patients with 3 to 10 adenomas, or any adenoma  $\geq 1$  cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years providing that piecemeal removal has not been performed and the adenoma(s) are removed completely; if the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years
4. Patients who have more than 10 adenomas at 1 examination should be examined at a shorter (<3 y) interval, established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome
5. Patients with sessile adenomas that are removed piecemeal should be considered for follow-up evaluation at short intervals (2-6 mo) to verify complete removal; once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment; completeness of removal should be based on both endoscopic and pathologic assessments
6. More intensive surveillance is indicated when the family history may indicate HNPCC

Risk stratification could reduce markedly the intensity of follow-up evaluation in a substantial proportion of patients, so that colonoscopy resources could be shifted from surveillance to screening and diagnosis. Risk stratification also could reduce the small, but finite, screening colonoscopy complication rate.<sup>22</sup> This set of guidelines is the latest in a series, begun in 1997, updated in 2003, and builds on the concept of change consistent with new evidence.<sup>13-16</sup> It incorporates the American College of Gastroenterology polyp guidelines from 2000.<sup>23</sup> Before the earlier-described guidelines, physicians had minimal guidance in managing postpolypectomy patients. Our goal is to provide a continuing basis for recommendations to guide postpolypectomy follow-up evaluation.

These guidelines (Tables 2 and 3) have been endorsed by the Colorectal Cancer Advisory Committee of the American Cancer Society and by the governing boards of the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.

**Table 3.** Additional Surveillance Considerations

1. The present recommendations assume that colonoscopy is complete to the cecum and that bowel preparation is adequate; a repeat examination should be performed if the bowel preparation is not adequate before planning a long-term surveillance program
2. There is clear evidence that the quality of examinations is highly variable; continuous quality improvement process is critical to the effective application of colonoscopy in colorectal cancer prevention
3. A repeat examination is warranted if there is a concern that the polyp was removed incompletely, particularly if it shows high-grade dysplasia
4. Endoscopists should make clear recommendations to primary care physicians about when the next colonoscopy is indicated
5. Given the evolving nature of guidelines, it is important that physicians and patients should remain in contact so that surveillance recommendations reflect changes in guidelines
6. Pending further investigation, performance of FOBT is discouraged in patients undergoing colonoscopic surveillance
7. Discontinuation of surveillance colonoscopy should be considered in patients with serious comorbidities with less than 10 years of life expectancy, according to the clinician's judgment
8. Surveillance guidelines are intended for asymptomatic people; new symptoms may need diagnostic work-up
9. The application of evolving technologies such as chromoendoscopy, magnification endoscopy, narrow band imaging, and computed tomography colonography are not established for postpolypectomy surveillance at this time

## Methodology and Literature Review

We performed a Medline search of the postpolypectomy literature under the subject headings "colonoscopy" and "adenoma," "polypectomy surveillance," and "adenoma surveillance," limited to English language articles from 1990 to 2005. This search identified 35 articles based on inclusion of data pertaining to baseline colonoscopy characteristics, advanced adenoma detection during follow-up surveillance, and advanced adenoma characteristics. Subsequently, we identified 12 additional articles from references of reviewed articles. Of these 47 articles we considered 13 to be relevant studies according to the following criteria: (1) colonoscopy studies specifically addressing the relationship between baseline examination findings and the detection of advanced adenoma or of any adenoma during follow-up colonoscopy; or (2) sigmoidoscopy studies, with large cohorts and follow-up periods longer than 10 years, specifically addressing the association between baseline examination findings and the detection of advanced adenomas during follow-up evaluation. After the initial review of published data, we added 1 relevant abstract and a newly published article to the review. These were studies that were identified by members of the guideline committee and for which the data were available to the committee. We excluded studies that included patients with inflam-

matory bowel disease, a prior history of colorectal cancer, and familial syndromes. Our final review was based on 15 studies that met the inclusion criteria.<sup>5,7,12,20,21,24-35</sup> The most recent publication for the outcome of interest (adenomas and advanced neoplasia) was used for studies with more than 1 publication. We gave separate listings to the St. Mark's study by Atkin et al<sup>7</sup> for the outcomes for colon cancer and for rectal cancer. Two studies reported only on risk factors for adenomas rather than for advanced adenomas at surveillance.<sup>32,34</sup>

The literature review was conducted by 2 independent authors (S.J.W. and J.S.S.). A third author (A.G.Z.) created the evidence table that was circulated among members of the US Multisociety Task Force on Colorectal Cancer and the American Cancer Society's Colorectal Cancer Advisory Committee. Recommendations in this report were based on the review of the evidence and the discussions at the combined meeting.

The appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)) was organized to include the elements of study design. Ideally the best study design would fulfill the following criteria:

1. Be a randomized controlled trial (RCT) or an observational cohort study of patients with adenoma(s) at baseline that were cleared by colonoscopy, after excluding people at high risk (such as familial syndromes).
2. Consider all the candidate risk factors.
3. Have sufficient follow-up time for adenomas to develop, with few drop-outs.
4. Have planned colonoscopic assessment for recurrence in all patients in the cohort.
5. Have enough outcome events for reasonable statistical precision and sufficient statistical power to detect associations between baseline characteristics and adenoma outcomes.
6. Present the analyses that include adjustment for multiple risk factors and consider what the independent effects are.

The appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)) includes classification of the type of design (RCTs or observational cohort studies), the number of patients at risk, the follow-up intervals recommended, and the length of time patients were followed-up. We also list the variables considered as risk factors and the effect of these factors on the incidence of subsequent adenomas or on advanced neoplasia. The multivariate estimate of the relative risk was presented whenever available. The definition of an advanced neoplasia is given for each study and varies considerably by

study. Summary comments on each study also are included.

Review of the evidence was confounded by variations in definitions, design of the studies, timing and multiplicity of surveillance intervals, and quality of the baseline colonoscopy (see the appendix in supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)). Because of these variations, the review of the literature cited was descriptive rather than a single summary value of risk (ie, meta-analysis) for all studies. The literature cited is grouped by type of study design: (1) RCTs in which the surveillance interval is set and maintained as much as possible although eligibility requirements may vary; (2) observational cohort studies that are primarily registry studies with more passive recruitment for surveillance. The RCTs provide stronger evidence for the timing of follow-up examinations because those who received surveillance colonoscopy were not a special subset of all enrolled. As noted earlier, relative risks or odds ratios (ORs) from multivariate analyses were presented in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)) whenever available. For 2 studies,<sup>7,21</sup> the measure of risk was the standardized incidence ratio (SIR) with adjustment for age and sex rather than a relative risk. In 1 study,<sup>12</sup> the hazard ratio is given as the measure of the effect. A descriptive graphic presentation was given with point estimates and confidence intervals for the relative risk for adenomas and advanced neoplasia by baseline adenoma characteristics of multiplicity, size, histology, high-grade dysplasia, and location. These descriptive plots (Figure 1) of the measure of the effect for various risk factors provide a summary of the number of studies reporting a measure of effect for a given risk factor and the consistency and magnitude of this factor on adenoma and advanced neoplasia recurrence. The review of evidence assessed the risk factors for adenomas and for advanced adenomas but the discussion concentrated on the factors affecting advanced adenomas. The definition of advanced adenoma differs from study to study.<sup>36</sup> The most encompassing definition included any adenoma sized 1.0 cm or larger, any villous component (ie, nontubular), high-grade dysplasia, or invasive cancer.

Given the concern in detecting colorectal cancers at surveillance, the number of colorectal cancers detected by time under surveillance is cited whenever these data were included in the published study. Special characteristics of the study population and selection for the cohort were also noted in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)).

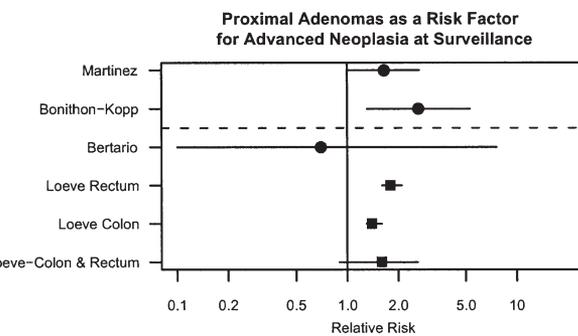
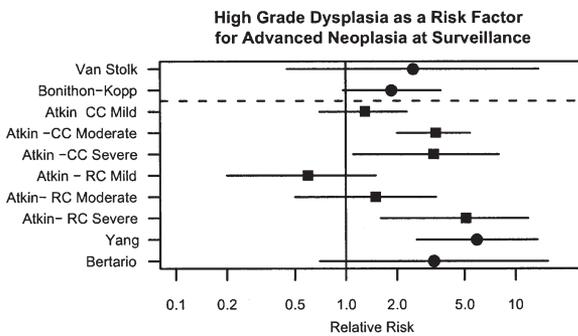
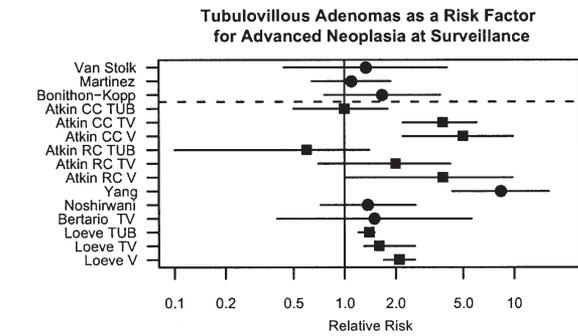
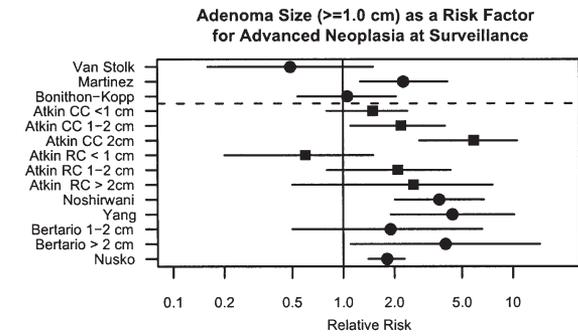
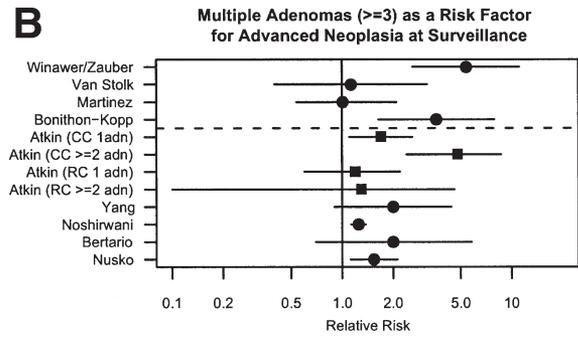
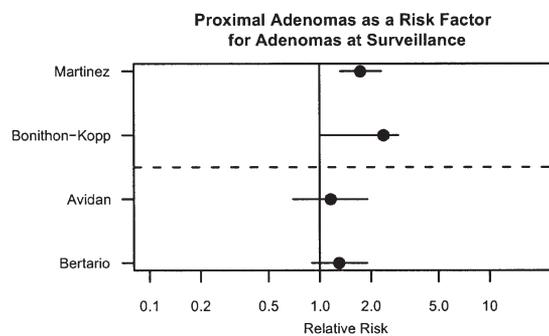
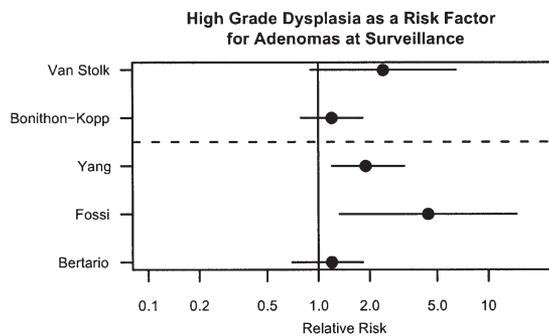
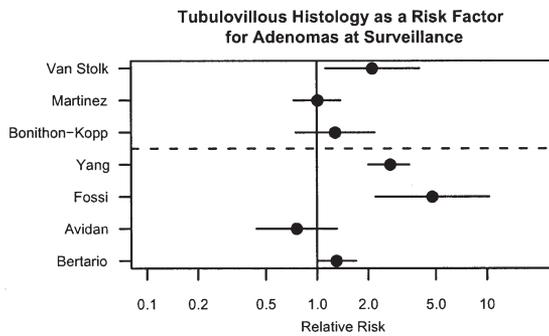
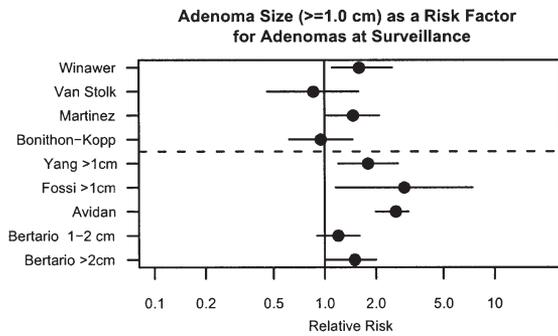
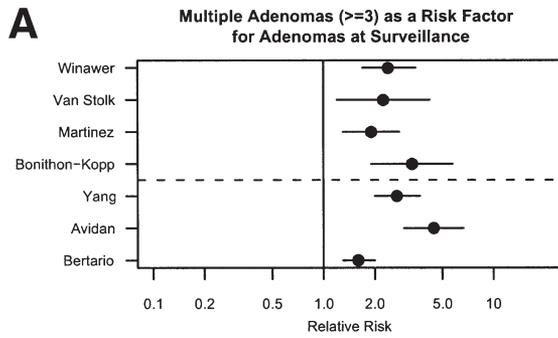
## Results of the Literature Review and Rationale for the Guidelines

Certain characteristics of colorectal adenomas at baseline colonoscopy are associated with the rate of adenoma detection and the histologic severity of subsequent adenomas. These data can be used as the basis for decisions about safe and effective postpolypectomy surveillance intervals by stratifying patients into lower-risk and higher-risk groups for future advanced adenomas. The available body of evidence is the basis for these recommendations.

### Quality of Baseline Colonoscopy

Baseline adenoma characteristics play a major role in determining appropriate postpolypectomy surveillance intervals. Characteristics of the baseline colonoscopy are also an important predictor for subsequent neoplasia. The baseline colonoscopy needs to be of high quality for the baseline adenoma characteristics to be used for planning surveillance intervals. As defined by the US Multi-Society Task Force, a high-quality colonoscopy reaches the cecum, has little fecal residue, and has a minimum time of withdrawal from the cecum of 6–10 minutes.<sup>37</sup> Baseline colonoscopy without a good clearing of the colon places the patient at increased risk for subsequent neoplastic findings.<sup>38</sup> Adenomas, advanced adenomas, and cancers are missed by colonoscopy.<sup>39–42</sup> Sensitivity could be increased by continuing quality improvement programs for the performance of colonoscopy.<sup>37</sup> Trials designed specifically to evaluate surveillance, in which colonoscopy is performed by experienced endoscopists, such as the National Polyp Study have shown that a low incidence of cancer can be achieved in postpolypectomy patients.<sup>5,25,43</sup> The National Polyp Study required meticulous clearing at the initial baseline with repeat colonoscopy if this was not achieved with high confidence.

On the other hand, studies designed for other purposes, such as the pooled chemoprevention studies reported by Robertson et al,<sup>20</sup> and community studies clearly show that higher miss rates commonly occur.<sup>39</sup> Incomplete removal of large sessile polyps, particularly by piecemeal polypectomy, could contribute to a higher subsequent incidence of a colon cancer as in the chemoprevention trials.<sup>20,44</sup> Atkin et al<sup>7</sup> also showed that inadequate removal of sessile rectosigmoid adenomas at baseline was associated with a marked increase in risk for rectal cancer in a rigid sigmoidoscopy study. The National Polyp Study exclusion of patients with sessile adenomas larger than 3.0 cm and provision for individualized follow-up evaluation for these patients could be



another factor that contributed to the low incidence of cancer during the follow-up period in this study.<sup>5</sup> Loeve et al<sup>21</sup> assessed colorectal cancer incidence after adenoma detection in Holland based on 78,473 patients and found that colorectal cancer incidence was not greatly reduced until 5–6 years after the initial diagnosis, and attributed the lack of earlier effect to inadequate removal of adenomas when initially diagnosed. It is therefore important to consider early and late-appearing cancers separately in postpolypectomy trials to separate true incidence reduction from missed cancers. This point is shown in the chemoprevention trials in which a large proportion of cancers were found early; this was probably caused in part by the inadequate removal of large adenomatous polyps. For example, 9 of 19 cancers in the study of Robertson et al<sup>20</sup> were found within 26 months of the initial colonoscopy.

### Characteristics of Baseline Adenomas as Predictors of Subsequent Advanced Adenomas

**Multiplicity.** Multiplicity at baseline has been shown to predict subsequent detection of advanced adenomas (see appendix in supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org) and Figure 1). Of the RCTs, the National Polyp Study,<sup>25</sup> the European fiber and calcium study,<sup>29</sup> and the pooled analysis of chemoprevention studies<sup>20</sup> showed that multiplicity conferred an increased risk for advanced neoplasia at surveillance. The pooled analysis did not report ORs but did report a significant difference in mean number of prior lifetime adenomas at baseline in those with and without advanced neoplasia at surveillance. Neither the wheat bran study described by Martinez et al<sup>28</sup> nor the chemoprevention study presented by van Stolk<sup>27</sup> noted a significant association between baseline multiplicity and the detection of advanced adenoma at follow-up evaluation. However, 35% of subjects in the study by Martinez et al<sup>28</sup> had prior

adenomas, so that prior colonoscopies may have reduced the number of adenomas detected at the index colonoscopy for study accrual. Van Stolk<sup>27</sup> showed that individuals with 3 or more adenomas at baseline were more likely than those with 1 or 2 adenomas at baseline to have an adenoma detected at surveillance (OR, 2.25; 95% confidence interval [CI], 1.20–4.21), but found no adenoma characteristic predictive of advanced adenomas at surveillance. They noted, however, that the study had limited power to detect risk factors for advanced neoplasia.

The observational cohort studies also showed that multiplicity was a risk factor for subsequent advanced adenomas and cancer. Atkin et al<sup>7</sup> followed-up a cohort of patients who initially had rectosigmoid adenomas removed but with no further intervention in the colon for an average of 13.8 years. They showed that having 2 or more rectosigmoid adenomas compared with 1 rectosigmoid adenoma at baseline was associated with an increased risk for subsequent colon cancer but not for subsequent rectal cancer. Noshirwani et al<sup>31</sup> reported that the number of adenomas at baseline was related to an increased risk (OR, 1.25; 95% CI, 1.13–1.38) for advanced adenomas at surveillance in a cohort from the Cleveland Clinic.

**Size.** Adenoma size larger than 1 cm also was shown to predict metachronous advanced adenomas in the wheat bran study.<sup>28</sup> However, the other 4 RCTs did not find adenoma size at baseline to be an independent predictor of advanced neoplasia at surveillance. Adenoma size was important in 7 of 8 of the observational cohort studies assessing advanced neoplasia. Loeve et al<sup>21</sup> did not present data on adenoma size. In a rigid sigmoidoscopy study, Atkin et al<sup>7</sup> reported that there was a significant trend ( $P < .002$ ) for increased risk for subsequent colon cancer with increasing size of the rectosigmoid adenoma at baseline. The standardized in-

**Figure 1.** These graphs show the associations between adenoma characteristics at baseline and subsequent risk for (A) adenomas and for (B) advanced adenomas or colorectal cancer. The dotted line separates the results from the RCTs of surveillance and chemoprevention from the results from the observational cohort studies. Within the 2 groupings the studies are listed by year published. The graphs are presented for the baseline risk factors of adenoma multiplicity ( $\geq 3$ ), adenoma size ( $\geq 1.0$  cm), adenoma histology (tubulovillous or villous), (A) high-grade dysplasia, and proximal location (B). The left column is for the risk with respect to adenomas at surveillance, and the right column is for risk with respect to advanced neoplasia. The studies differ with respect to the classification levels of the risk factors and on the definition of advanced neoplasia. The specification of each study is given in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)). The studies also cover different periods of follow-up evaluation and use different measures of effect such as ORs, relative risks, hazard ratios, and SIRs as noted in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)). The term *relative risk* is used on the horizontal axis of the figure to represent these different measures of effect. The referent category for the ORs, relative risks, and hazard ratios is the lowest risk category. These estimates are denoted by black circles. Multivariate estimates are used when available. In 2 studies,<sup>7,21</sup> SIRs were reported and are denoted by black squares. The referent category for the SIR is the general population. Note that Avidan et al<sup>34</sup> and Noshirwani et al<sup>31</sup> used the number of adenomas, not more than 3 adenomas. CC, colon cancer; RC, rectal cancer. Relative risk represents the OR, relative risk, hazard ratio, or SIR as summarized for each study in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)).

idence ratio for colon cancer was 1.5 (95% CI, 0.8–2.4) in patients with baseline adenomas less than 1 cm in size, increased to an SIR of 2.2 (95% CI, 1.1–4.0) for 1- to 2-cm adenomas, and further increased to an SIR of 5.9 (95% CI, 2.8–10.6) for adenomas larger than 2 cm. Increasing size of the rectosigmoid adenomas at baseline also showed a significantly increasing trend of an increase in SIR for rectal cancer even though the individual SIRs for rectal cancer by adenoma size were not statistically different from the general population risk. Yang et al,<sup>30</sup> also in a sigmoidoscopy study, showed that larger adenoma size was related to subsequent risk for advanced neoplasia at surveillance with an RR of 2.4 (95% CI, 1.3–4.6) for size 0.6–1.0 compared with size 0.5 cm or smaller and an RR of 4.4 (95% CI, 1.9–10.2) for size greater than 1.0 cm at baseline. Noshirwani et al<sup>31</sup> showed that a baseline adenoma of 1 cm or larger compared with less than 1 cm conferred an OR of 3.68 for subsequent advanced neoplasia. Bertario et al<sup>12</sup> found that patients with adenomas larger than 2 cm compared with 2 cm or smaller at baseline had a hazard ratio of 4.0 (95% CI, 1.1–14.4) for the development of follow-up advanced adenomas. Lieberman and Weiss,<sup>24</sup> reporting the 5-year follow-up results from the VA Cooperative Study 380, found that the percentage of patients with advanced neoplasia was higher in those with baseline adenomas of 1.0 cm or larger (2.6%) compared with those less than 1.0 cm (0.4%) over 5 years of surveillance. Although the majority of studies reported size to be a significant factor, some did not. Neither van Stolk<sup>27</sup> nor Bonithon-Kopp<sup>29</sup> found size to be a significant predictor of metachronous advanced adenomas. Incomplete removal of large polyps identified at baseline could be a reason that larger size was a strong predictor of subsequent advanced neoplasia in these studies.

**Histology.** Histologic type of adenoma at baseline was not a significant predictor of advanced neoplasia in the randomized trials but was for several of the observational cohorts. Histology is a particularly difficult predictor to evaluate because of the somewhat subjective nature of classifying tubular, tubulovillous, and villous adenomas.<sup>45</sup> Atkin et al,<sup>7</sup> in a rigid sigmoidoscopy study, showed that tubulovillous histology at baseline was associated with an SIR of 3.8 (95% CI, 2.2–6.0) and villous histology had an SIR of 5.0 (95% CI, 2.2–9.9) for the detection of subsequent colon cancer. Histology at baseline was also an important predictor for subsequent rectal cancer risk in this study. In another sigmoidoscopy study, Yang et al<sup>30</sup> reported that villous or tubulovillous histology at baseline conferred an RR of 8.34 (95% CI, 3–16.0) for the detection of advanced neoplasms (rectal cancer, or adenoma with severe dysplasia) at follow-up

evaluation. Loeve et al<sup>21</sup> reported a significant trend for increasing risk for colorectal cancer at surveillance in relationship to increasing villous component or carcinoma in situ compared with tubular histology.

High-grade dysplasia is related to larger adenoma size and villous component at baseline and is an important predictor for subsequent advanced neoplasia in 3 of the observational cohort studies.<sup>7,24,30</sup> By definition all adenomas have some level of dysplasia. In the past, dysplasia has been classified as mild, moderate, severe, or carcinoma in situ. Currently, severe dysplasia or carcinoma in situ are considered the equivalent of high-grade dysplasia and mild or moderate dysplasia are considered the equivalent of low-grade dysplasia. For the purposes of this analysis, wherever possible, the risks are assessed for high-grade and low-grade dysplasia. Atkin et al<sup>7</sup> found an increasing degree of dysplasia was associated with an increasing risk for subsequent colon cancer with an SIR of 3.3 (95% CI, 1.1–8.0) for severe dysplasia in baseline adenomas. Yang et al<sup>30</sup> reported ORs of 5.9 (95% CI, 2.6–13.5) and 14.4 (95% CI, 5.0–41.4), respectively, for the development of subsequent advanced neoplasia (rectal cancer or severe dysplasia) in patients with moderate and severe dysplasia at baseline. Lieberman and Weiss,<sup>24</sup> in the VA Cooperative Study, determined that 10.9% of patients with high-grade dysplasia in adenomas of any size at baseline had advanced neoplasia over the 5-year surveillance period compared with 0.6% in those with tubular adenomas less than 1.0 cm lacking high-grade dysplasia.

**Location.** Martinez et al<sup>28</sup> reported that a proximal adenoma at baseline was associated with an increased risk for subsequent advanced adenomas. The OR was 1.65 (95% CI, 1.02–2.67) for baseline proximal adenomas only vs distal adenomas only, and the OR was 2.69 (95% CI, 1.34–5.42) for proximal and distal adenomas vs distal adenomas only at baseline. Similarly, Bonithon-Kopp et al<sup>29</sup> reported an OR of 2.63 (95% CI, 1.31–5.3) for subsequent advanced neoplasia for patients with a proximal compared with no proximal location of baseline adenomas.<sup>29</sup> In the observational cohort study of Loeve<sup>21</sup> using large registry databases, the risk of colorectal cancer at surveillance was slightly lower for patients with colon adenomas at baseline than rectal adenomas.

**Other risk factors: patient age, sex, history of polyps, and family history of colorectal cancer.** In their RCTs, Martinez et al<sup>28</sup> and Bonithon-Kopp et al<sup>29</sup> reported an increasing risk for subsequent neoplasia with increasing age. Age was used frequently as a control variable in the analyses without an explicit risk factor presented for the age effect. Martinez et al<sup>28</sup> and Bonithon-Kopp et al<sup>29</sup> reported an increased risk for men for

advanced neoplasia at surveillance. Sex also was used frequently as a control variable in the analyses without an explicit risk factor presented for the sex effect.

Both Martinez et al<sup>28</sup> and Bonithon-Kopp et al<sup>29</sup> noted that a history of polyps before the baseline adenoma was associated with an increased risk for advanced neoplasia at surveillance. Although it is not always possible to determine whether prior polyps are adenomatous polyps, the presence of prior polyps can be considered as an additional risk factor. The effect of prior adenomas or other polyps on subsequent risk was not considered in all studies. When noted in the reviewed studies, the percentage of patients in a study with prior adenomas or other prior polyps is included in the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)).

Family history of colorectal cancer and adenomas at a young age<sup>46</sup> is an established risk factor for the development of colorectal cancer.<sup>47–49</sup> However, few studies have addressed specifically the relationship between family history and metachronous advanced adenomas in post-polypectomy patients. The National Polyp Study showed that a family history of colorectal cancer in patients age 60 or older predicted a 4.8-fold increased risk for advanced adenomas at follow-up evaluation.<sup>26</sup> Fossi et al<sup>32</sup> noted that a family history of colorectal cancer in a first-degree relative was a risk factor for adenomas at surveillance, but the study did not report on risk factors for advanced adenomas at surveillance. As noted previously, Martinez et al<sup>28</sup> and Bonithon-Kopp et al<sup>29</sup> both reported proximal adenomas at baseline as predictors of subsequent advanced neoplasia. Proximal adenomas are associated with family history of colorectal cancer.<sup>49</sup> It is possible that these studies also might have had an increased risk for advanced adenoma because of the association of family history of colorectal cancer with proximal adenomas.

**Summary of baseline predictors.** The totality of evidence suggests that multiplicity ( $\geq 3$  adenomas), size ( $\geq 1$  cm), villous features, and high-grade dysplasia are predictors of future advanced adenomas or cancers. Family history and proximal location also may predict metachronous advanced adenomas, but have not been well studied. Analysis of the relative importance of each of these predictors is complicated by their interrelationships. Consequently, multivariate analysis for some studies may find that size and histology<sup>45</sup> are the most important whereas others may report that multiplicity is the most important.

There is a consensus among many of the studies that the group at lower risk for subsequent advanced adenomas has only 1 or 2 adenomas, all less than 1 cm in size with no high-grade dysplasia or villous features. The risk

for colon cancer in such low-risk patients, over an average of 14 years, has been shown in a rigid sigmoidoscopy polypectomy study to be similar to the average-risk population.<sup>7</sup>

In colonoscopy studies patients have been followed-up for only 5–6 years after colonoscopic polypectomy to assess their subsequent risk for neoplasia.<sup>24,25</sup> Sigmoidoscopic polypectomy without colonoscopic assessment is insufficient to establish colonoscopic surveillance intervals. In the Atkin et al<sup>7</sup> study, colon risk was assessed in an anatomic area where polypectomy was not performed (ie, above the rectosigmoid). Postpolypectomy surveillance guidelines ideally should be based on colonoscopic follow-up evaluation of patients who have had colonoscopic polypectomy. Based on the available evidence, we can project that apparently low-risk patients can wait 5 and possibly 10 years for repeat colonoscopy. However, further evaluation of this low-risk group is required to confirm the safety of these intervals.

For rarer events such as colorectal cancer at surveillance, and even for adenomas in the smaller studies, the confidence intervals on colorectal cancer or advanced neoplasia may be relatively wide. Consequently, a non-statistically significant result does not rule out that this factor has no impact on risk for surveillance findings.

## Discussion

These guidelines are based on all of the available evidence, clinical experience, knowledge of the adenoma-carcinoma sequence, and expert opinion. They are intended to be used by clinicians as a guide in their approach to postpolypectomy surveillance, taking into consideration clinical judgment in patient comorbidities, patient preferences, and family history. The differences between these guidelines and prior ones are shown in Table 1. The detailed evidence for these guidelines are presented in the literature review summarized by the appendix (see supplemental material online at [www.gastrojournal.org](http://www.gastrojournal.org)) and Figure 1.

There is strong evidence that the adenoma cohort can be stratified according to the risk for development of subsequent advanced adenomas. Recommendations for surveillance intervals in persons with multiple adenomas and those with advanced adenomas are based primarily on the National Polyp Study,<sup>25</sup> an RCT, and observational cohort studies. Recommendations in the low-risk group of 1 to 2 small tubular adenomas are based on the low incidence of advanced adenomas in observational cohort studies and the National Polyp Study<sup>25</sup> over 3- to 6-year intervals and the observation by Atkin et al<sup>7</sup> that persons with small tubular adenomas are not at increased

risk for developing colorectal cancer. In our opinion, the data from observations of cohort studies supports an interval of at least 5 years in this low-risk group; however, we reasoned that based on the data from Atkin et al,<sup>7</sup> informed physicians and their patients could conclude that a 10-year interval, similar to that used in the average-risk population, also would be acceptable. The recommendation to perform short-interval follow-up evaluation in patients with 10 or more adenomas is based on the increased probability of missed lesions in patients with numerous adenomas. The recommendation to perform very short interval follow-up evaluation in patients with large sessile polyps removed piecemeal is the repeated observation that a significant fraction of these polyps are removed incompletely by the initial polypectomy. Recommended intervals in hereditary nonpolyposis colorectal cancer (HNPCC) are based on the known rapid transformation through the adenoma carcinoma sequence in these patients.<sup>50</sup>

The present collaborative effort between the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society was based on several considerations. The gradual increase in screening and the marked increase in screening colonoscopy are creating a large subset of the population that will require surveillance based on adenoma detection. Both societies felt the need to update the guidelines for the follow-up of these patients, according to the latest evidence. Recent surveys have shown that 50% of endoscopists are not following previously published guidelines for postpolypectomy surveillance.<sup>51,52</sup> It was believed that a consensus by the 2 organizations would strengthen the recommendations and increase their use.

From the 1970s to the 1990s, annual follow-up colonoscopy was common practice after polypectomy and there were no guidelines available that addressed how clinicians should best follow-up these patients. In 1993, a report from the National Polyp Study showed that it was safe to defer the first follow-up examination for 3 years.<sup>25</sup> This evidence, along with the knowledge of the long natural history of the adenoma-carcinoma progression, led to guidelines in 1997 that recommended a 3-year interval for the first follow-up examination after removal of adenomas.<sup>15,16</sup> Practice began to evolve along the lines of this evidence. Guidelines have been used in the courts of law as indicating the standard of practice.<sup>53</sup>

Recent guidelines have introduced the concept of risk stratification of patients at the time of polypectomy into those more likely or less likely to develop subsequent serious neoplasia.<sup>13</sup> In addition, the concept of the advanced adenoma as a surrogate biological indicator of cancer risk has been adopted.<sup>36</sup> Colorectal cancer would

be a more ideal outcome measure. However, the advanced adenoma was adopted as an early outcome measure of efficacy because a much longer period of time would be required for conclusions to be drawn if cancer were used as the outcome measure. This reasoning is supported by several studies that have shown the relationship between advanced adenomas and cancer.<sup>45,54,55</sup> A uniform definition of the advanced adenoma has not yet been established clearly, but most include adenomas with a size 1 cm or larger, any villous histology, or high-grade dysplasia.

Several studies have examined factors that could predict the future risk for advanced adenomas including: number, size, histology, and location of baseline adenomas; patient age; and family history of colorectal cancer. Most of the studies that assessed risk factors for advanced adenomas at surveillance either were RCTs of surveillance,<sup>25</sup> chemoprevention trials,<sup>20,27–29</sup> a prospective surveillance study,<sup>24</sup> or registry-based observational cohort studies of patients returning for surveillance with less-structured follow-up evaluation outside the context of a clinical trial.<sup>7,12,21,30,31,33,35</sup> The most consistent evidence for predicting subsequent advanced adenomas indicates that multiplicity, size, villous histology, and high-grade dysplasia are the important factors at baseline. Based on these factors, patients can be stratified at the time of colonoscopy into lower or higher risk for subsequent advanced adenomas. The strongest studies for evaluating predictive factors for future neoplasia after polypectomy are those designed specifically as postpolypectomy surveillance studies such as the National Polyp Study. Chemoprevention randomized trials were designed to assess the drug intervention effect with less of an emphasis on determining optimal surveillance intervals.

Patients who have had a polypectomy and long-term surveillance have been shown to have a reduced incidence of colorectal cancer.<sup>5–12</sup> When one separates out the effect of initial polypectomy from the subsequent surveillance, modeling has shown that more than 90% of the reduced incidence over the first 5–6 years is the result of the initial polypectomy. However, there is a subgroup that can be identified as having a higher risk for subsequent cancer by using the advanced adenoma as a surrogate marker.<sup>56</sup> These observations support the concept of stratifying patients by baseline factors so that the group at increased risk can be identified for more intensive surveillance and the group at lower risk can be identified for less intensive surveillance. Reduction in the intensity of surveillance could free up endoscopic resources that could be shifted to screening and diagnosis, thereby increasing the benefit and reducing the procedural risk.

The use of fecal occult blood testing (FOBT) after colonoscopy in postpolypectomy patients has been reported to be a widespread practice (38% of patients had FOBT after adenoma removal at colonoscopy).<sup>57</sup> The National Polyp Study has shown that the use of FOBT after colonoscopy results in a substantial number of unnecessary colonoscopies; 77% of colonoscopies performed to evaluate positive surveillance FOBT results detected no advanced adenomas or cancer (ie, the positive predictive value was 23%).<sup>58</sup> In a recent report by Bampton et al<sup>59</sup> of 785 patients who had a recent surveillance colonoscopy, the positive predictive value for an immunochemical FOBT was 27%. This was in a high-risk cohort composed of patients with a history of colonic neoplasia or with a strong family history. A lower positive predictive value would be expected in a lower-risk population. The possible benefit of FOBT in patients having surveillance colonoscopies needs further study, but with the present available evidence this should be discouraged.

In the present guidelines, recommendations for the lower risk group are intentionally flexible because follow-up colonoscopy studies are limited to 5–6 years.<sup>24,25</sup> Some physicians and patients may elect to have a follow-up colonoscopy at 5 years because they wish to be assured that future risk has been reduced to less than that of the average-risk population. Others may feel confident that this risk already has been reduced to less than that of the general population by adequate clearing of the colon and would be satisfied with either a 10-year follow-up colonoscopy or choosing other screening options currently recommended for individuals at average risk.<sup>13,14</sup>

Risk stratification and recommended follow-up intervals are based on the presumption that a high-quality colonoscopy was performed at baseline. However, variable colonoscopic miss rates for adenomas and cancer have been shown.<sup>5,20,39–42,60–62</sup>

This variability in colonoscopic baseline quality could translate into either a lower rate of subsequent cancers detected during surveillance as in the National Polyp Study,<sup>5,62</sup> or a higher rate as seen by Robertson et al<sup>20</sup> and others<sup>39,61</sup> For example, in the National Polyp Study, if the baseline colonoscopy did not clear the colon with high confidence (excellent preparation, complete polypectomy), the examination was repeated before entering the patient into the surveillance program. Repeat examinations were required in 13% of the patients.<sup>25</sup> Such rigor contributed to a marked reduction in colorectal cancer incidence in the National Polyp Study that was not observed in other studies.<sup>20,39,61</sup> In Australian and Japanese studies<sup>60,62</sup> the low miss rates were calcu-

lated only from patients in whom the cecum was intubated. In 1 study of missed cancers,<sup>39</sup> failure to intubate the cecum accounted for some undetected cancers.

The quality of the baseline examination can be evaluated to some extent by the number of cancers detected earlier vs later in a surveillance program. Thus, the major benefit of the baseline colonoscopic polypectomy rests on the quality of that examination.<sup>37,38</sup> The concern by clinicians of missed cancers can be assuaged by high-quality baseline performance of colonoscopy. Protection can never be 100%, but it is high (76%–90% colorectal cancer incidence reduction) with high quality examination.<sup>5,37,63</sup>

There was insufficient evidence to include family history in the guidelines as a predictor of metachronous advanced adenomas. Clearly, however, family history of colorectal cancer in a close relative does increase the risk for colorectal cancer in other relatives and needs further study in the postpolypectomy setting.<sup>47–49</sup> Issues such as this must be considered on an individual basis when clinicians are determining appropriate follow-up evaluation.

Patients with a family history indicating HNPCC require special screening and surveillance.<sup>13,15,49</sup> HNPCC is an autosomal-dominant inherited cancer syndrome that accounts for 1%–5% of colorectal cancer cases and is caused by germ-line mutations in 1 of 5 mismatch repair genes. The mean age for colorectal cancer development in HNPCC is 44 years. Cancers tend to be right sided and often are poorly differentiated, mucus-producing tumors with intense lymphocytic infiltrates. Tumors show microsatellite instability (MSI) and immunostaining often is negative for one of the mismatch repair gene products. There are no clinical criteria that are perfectly sensitive for HNPCC. The modified Bethesda criteria perform best in this regard.<sup>64</sup> HNPCC should be suspected when colorectal cancer or other tumors with relative specificity for HNPCC (endometrial, ovarian, small bowel, ureter, or renal pelvis) occur in younger people, when multiple relatives and generations are affected, or when tumor location and histology are suggestive. Potentially affected persons can be screened by testing their tumors for microsatellite instability or for mismatch repair gene products by immunostaining. Genetic testing is used when these screening tests are positive or when the clinical presentation and family history are very strongly suggestive. Tumors in HNPCC move through the adenoma-carcinoma sequence more rapidly than sporadic tumors.<sup>50</sup> Definite or potential gene carriers are screened by colonoscopy every 2 years beginning at age 20–25 years until age 40 years, and then annually.<sup>13</sup> Surveillance recommendations are

essentially the same as screening. The colon must be cleared carefully and complete polypectomy is essential, particularly for advanced adenomas. Patients who develop advanced adenomas and proven gene carriers can be offered prophylactic subtotal colectomy followed by annual proctoscopy and polypectomy.

Other issues evolving in the literature that require further study and may affect future guidelines include different recommendations for men and for women by age.<sup>65</sup> Given the evolving nature of guidelines, it is important that physicians and patients remain in contact so that surveillance practices will reflect changes in guidelines.

The management of patients with hyperplastic polyps only was omitted from prior guidelines. There is no evidence that patients with small distally located hyperplastic polyps have an increased risk for colorectal cancer and therefore they should be prescreened as appropriate for average-risk patients.<sup>66,67</sup> The present guidelines state this explicitly. It has been shown recently, however, that hyperplastic polyps are not a homogenous histologic category and there is accumulating evidence from molecular genetic studies that some histologic variants of hyperplastic polyps may evolve into a unique type of adenoma that resembles a hyperplastic polyp with dysplasia, called a *serrated adenoma*.<sup>68</sup> This type of adenoma in turn has been linked to the ultimate development of sporadic microsatellite instability adenocarcinoma. This form of colonic adenocarcinoma shares with HNPCC the genetic attribute (in this case, acquired) of microsatellite instability (sporadic microsatellite instability cancers) because of mismatch repair deficiency. Hyperplastic polyps at risk for such a progression show atypical architectural and cytologic features, often are large, sessile, and usually are located proximally. Other terms for these hyperplastic polyp variants are *sessile serrated adenoma* or *serrated polyp with abnormal proliferation*. Some investigators have suggested that complete removal and surveillance, as for typical adenomas, may be warranted in these cases.<sup>69,70</sup>

All endoscopists must remain alert to the syndrome of hyperplastic polyposis. Hyperplastic polyposis was defined by Burt and Jass<sup>71</sup> for the World Health Organization International Classification of Tumors as: (1) at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 1 cm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size distributed throughout the colon. Studies have found an increased risk for colorectal cancer in these patients.<sup>72,73</sup>

The pathway may be through the serrated adenoma.<sup>69,74,75</sup> The magnitude of the increased risk has not been determined. A recent case series of 15 patients found no cancer developed within 3 years of follow-up evaluation.<sup>76</sup> The optimal management of hyperplastic polyposis has not yet been defined and requires further study.

Technologic advances such as computed tomography colonography (also known as *virtual colonoscopy*, which uses computed tomography scan technology), chromoendoscopy (endoscopy with dye spraying of the mucosa), narrow band imaging (a high-resolution endoscopic technique that enhances the fine structure of the mucosal surface without dye), and magnification endoscopy (real-time magnification of endoscopic images) may one day be shown to be important in postpolypectomy surveillance.<sup>77–81</sup> Some of these techniques may have a special role in detecting flat adenomas.<sup>82,83</sup> However, at this time, there is insufficient evidence that any of these techniques should be part of routine postpolypectomy surveillance.

In summary, guidelines are dynamic and based on the evidence currently in the literature, understanding of the adenoma carcinoma sequence, and expert opinion. Guidelines must be updated as new evidence becomes available. The committee identified a number of areas of uncertainty and considers the following to be among the important questions for further study.

### Questions to Be Addressed

1. What are the reasons that guidelines are not followed more widely?
2. How can adherence to quality control indicators at baseline colonoscopy be encouraged to reduce the miss rate of advanced adenomas and colorectal cancers?
3. Will emerging studies with longer colonoscopy follow-up times support the safety of lengthening surveillance intervals?
4. What is the appropriate management and surveillance of the hyperplastic polyposis syndrome?
5. What is the appropriate surveillance of patients who have had an adenoma removed in piecemeal fashion?
6. Which definition of advanced adenoma is associated most strongly with subsequent cancer?
7. In the setting of postpolypectomy surveillance, what is the role of family history in predicting advanced adenomas and colorectal cancer?
8. What roles will chromoendoscopy, magnification endoscopy, narrow band imaging, and computed

tomography colonography play in postpolypectomy surveillance?

9. How can molecular genetic information help to stratify risk in patients with adenomatous polyps?
10. How can access to colorectal cancer screening and appropriate surveillance be increased?
11. What is the usefulness of guaiac-based, or immunochemical FOBT, in postpolypectomy surveillance?
12. What is the usefulness of stool DNA mutation testing in postpolypectomy surveillance?
13. What is the importance of detecting flat adenomas?
14. What is the importance of detecting serrated adenomas?
15. How do new insights in link between serrated polyps and microsatellite instability cancers impact surveillance practices?
16. What surveillance guidelines are appropriate for patients with atypical hyperplastic polyps, particularly if large, proximally located, or multiple, and serrated adenomas?

## Appendix

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1053/j.gastro.2006.03.012](https://doi.org/10.1053/j.gastro.2006.03.012).

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Address requests for reprints to: Sidney J. Winawer, MD, Gastroenterology and Nutrition Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021. e-mail: winawers@mskcc.org; fax: (212) 639-2766.