IRG was fair and appropriate. The advisory council then makes a funding recommendation to the institute. Decisions about funding are made by institute staff largely on the basis of the priorities assigned by the IRG and the advisory council, as well as the funds available for the specific type of research under consideration. Over the past 30 years the rate of approval of grant applications, depending on the institute, has varied from a low of 1 out of 10 or 12 applications to a high of 1 out of 3 or 4.

The system works remarkably well. Proposed projects must be innovative and rigorous in order to receive a score high enough to lead to funding. Applications that do not clearly lead the field are usually not approved. Grants are awarded for finite time periods. Once their research project has been funded, investigators know that the clock is ticking and that they must produce real results if their grants are to be renewed. The goal is to get the work done and the results published, so that the field is advanced and progress can continue. Wisely, the NIH requires remarkably little information, only a brief annual progress report, from investigators during the period covered by an award; the rationale for this approach is that progress will speak for itself. On the other hand, the institution receiving the funds must supply detailed records to the NIH during the funding period, ensuring that the monies are being expended to achieve the research goals.

Some grants are extremely productive, generating effective new therapies for difficult-to-treat illnesses, innovative ways to solve problems in health care delivery, and strategies to stem the spread of disease. Others are less so. However, most grants lead to discovery and to useful information. Investigators who are not productive are not re-funded. The unique success of the widely appreciated and emulated NIH peer-review process is that it rewards excellence and research productivity.

The NIH system for vetting investigator-initiated research is rigorous and comprehensive, identifying and funding the most meritorious work. Once grants are awarded, investigators should be left to focus on their work and should not be diverted by wasting time responding to the whims of interest groups. Only through a broadly based research program can we advance the health of all citizens. The NIH has a record of doing this well. The gem of worldwide biomedical research should not be rubbed in political dirt.

Drs. Drazen and Ingelfinger report having received grants from the National Institutes of Health. Dr. Drazen serves on the Advisory Council of the National Heart, Lung, and Blood Institute.

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Screening Virtual Colonoscopy — Ready for Prime Time?

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Many professional societies in the United States recommend screening for colorectal cancer in asymptomatic, average-risk adults, beginning at 50 years of age. Screening achieves two goals: the detection of early-stage nonmetastatic cancers that are surgically curable and the identification and removal of benign adenomatous polyps, the precursor lesions of nearly all adenocarcinomas. Several approaches to screening are available, ranging from the least expensive and least invasive, fecal occult-blood testing, to the more costly and invasive procedures — flexible sigmoidoscopy, barium enema, and colonoscopy. Each of these tests has inherent strengths and weaknesses related to cost, risk, sensitivity, specificity, and availability.[1]

Fiberoptic colonoscopy, the current gold standard for screening against which other tests are usually compared, provides very high sensitivity (>90 percent), with a false-negative rate of approximately 6 percent for adenomas of 1 cm or more in diameter.[2] Flexible sigmoidoscopy is unacceptable to some physicians and their patients because it screens only the left side of the colon. Barium enema may be recommended as an adjunct to flexible sigmoidoscopy for the evaluation of the proximal portion of the colon that lies beyond the reach of the sigmoidoscope. Colonoscopy has substantial drawbacks as a screening test, including the need to insert an intravenous catheter for the administration of sedatives, a recovery time of 30 to 60 minutes, and the requirement for a driver to accompany the patient home. The total time for admission, the performance of the procedure, and monitoring afterward is approximately two hours. Colonoscopy is

expensive, must be performed by an experienced specialist, and carries risks of bleeding, perforation, side effects of sedatives, and other complications, although most consider the level of risk to be acceptable. Another problem is the relatively low yield for an invasive test. Approximately 85 percent of screening colonoscopies identify no clinically significant pathology.[3,4] As many patients will attest, colonoscopy can be quite uncomfortable, and some patients complain that the bowel-cleansing preparation is worse than the procedure itself. Only a third of Americans older than 50 years of age have been screened with sigmoidoscopy or colonoscopy.[5] In contrast, 90 percent of women have had at least one Papanicolaou test for cervical cancer,[6] even though considerably fewer women die from cervical cancer than from colon cancer.

Virtual colonoscopy (or computed tomographic [CT] colonography) was first described in 1994 as a noninvasive test for the examination of the colonic lumen for polyps and cancers.[7] The test requires the same bowel-cleansing preparation as conventional colonoscopy, as well as the insertion of a rectal tube and the insufflation of air or carbon dioxide to distend the colon. Sedation is not required, and the time required for the procedure is approximately 10 to 15 minutes, with an additional 15 to 30 minutes for the interpretation of the study. Typically, two-dimensional CT images are examined and can be further processed with the use of commercially available software programs to render a three-dimensional display of the colonic lumen. Virtual images of the entire colon can be examined segment by segment, much as they are during conventional colonoscopy, in order to visualize the entire colonic mucosa.

Most studies of virtual colonoscopy to date have involved symptomatic patients or patients with a moderate-to-high risk of colonic neoplasia who underwent virtual and conventional colonoscopy on the same day.[8,9] In general, the two techniques have shown similar sensitivity and specificity for all lesions of at least 10 mm in diameter. Until now, the moderate sensitivity and specificity of virtual colonoscopy in populations with a low prevalence of colorectal neoplasia[10,11] and the wide range of sensitivities found even in populations with a high or moderate prevalence of such neoplasia[8,9,12] have raised doubts about its potential for screening for cancer. Factors such as suboptimal preparation of the colon, the limited experience with this new procedure among radiologists, and operator dependence as reflected by high interobserver variability all diminish its performance and reproducibility. The currently accepted clinical uses of virtual colonoscopy include the evaluation of patients who have undergone incomplete conventional colonoscopy, patients with obstructing colorectal cancer, and patients whose medical problems make them unsuitable for conventional colonoscopy; current uses generally do not include the screening of asymptomatic persons.

In this issue of the *Journal*, Pickhardt and colleagues[13] report the largest prospective evaluation to date of virtual colonoscopy as a colorectal screening test; the study involved 1233 asymptomatic adults who underwent virtual colonoscopy and same-day conventional colonoscopy. More than 97 percent of the subjects were at average risk for colorectal neoplasia. Six experienced radiologists based at three medical centers performed virtual colonoscopic examinations using a three-dimensional endoluminal display for the initial detection of polyps. Each patient underwent conventional colonoscopy performed by an experienced colonoscopist who, after the visualization of each colonic segment, was shown the results of the patient's virtual colonoscopy for that segment; the endoscopist could then reexamine each segment if those results suggested that polyps measuring at least 5 mm in diameter had been missed on conventional colonoscopy.

Adenomas 10 mm or more in diameter were found in 3.9 percent of patients, and two contained adenocarcinoma. The sensitivity of virtual colonoscopy in an analysis according to the polyp was 92.2 percent for adenomatous polyps of 10 mm or larger, 92.6 percent for adenomatous polyps of 8 mm or larger, and 85.7 percent for adenomatous polyps of 6 mm or larger, as compared with 88.2 percent, 89.5 percent, and 90.0 percent, respectively, for conventional colonoscopy performed by colonoscopists who were unaware of the results on virtual colonoscopy. The negative predictive value of normal findings on virtual colonoscopy was more than 99 percent for polyps of at least 8 mm. If a threshold polyp size of 10 mm had been used, 7.5 percent of the patients who underwent virtual colonoscopy would have required referral for polypectomy; with a threshold of 8 mm, the proportion would have been 13.5 percent; and with a threshold of 6 mm, it would have been 29.7 percent. Virtual colonoscopy identified 55 polyps of 5 mm or more in diameter that were not detected on initial colonoscopy, 21 of

which were adenomatous and at least 6 mm in diameter, including one 11-mm malignant polyp. The average time spent by patients undergoing virtual colonoscopy was 14 minutes — approximately half that required for conventional colonoscopy — and the average time required for the interpretation of virtual colonoscopic studies was less than 20 minutes. Virtual colonoscopy also permitted the detection of five asymptomatic cancers outside of the colon, as well as aortic aneurysms and renal and gallbladder calculi.

A number of factors may explain these impressive results. First, it is worth noting that the technique described by Pickhardt and colleagues differs from that used in previous studies. The authors used water-soluble and barium contrast material to tag residual fluid and retained stool, thereby enabling the imaging software to digitally remove all opacified fluid and stool from the image by a process known as electronic cleansing. All virtual colonoscopic studies were performed with the use of multidetector CT scanners, which permit faster, higher-resolution imaging than the single-detector scanners that have been used previously.

Second, the calculation of the sensitivity of virtual colonoscopy was based on the 210 adenomas of 6 mm or more in diameter and did not include the 134 nonadenomatous (mostly hyperplastic) polyps 6 mm or larger that were detected. The authors classified nonadenomatous polyps as false positive results, because they are not associated with the risk of cancer and are not the target of screening. Most virtual colonoscopic studies define all polyps, not just adenomas, as true positive findings. Some studies have suggested that the rate of detection of hyperplastic polyps with virtual colonoscopy is lower than that for adenomas,[8,9] possibly because the former are more likely to be effaced when the colon is distended with air. Consequently, the exclusion of hyperplastic polyps may have resulted in higher estimates of the sensitivity of virtual colonoscopy. At the same time, the classification of hyperplastic polyps as false positive findings resulted in lower estimates of the specificity of virtual colonoscopy.

Finally, the authors suggest that their use of a primary three-dimensional approach for the detection of polyps rather than the currently accepted two-dimensional approach with three-dimensional imaging used only to resolve uncertainties may have contributed to their high detection rates.[14,15] Alternatively, their excellent results may reflect the vigorous bowel preparation and electronic cleansing, rather than the nature of their interpretive technique. Indeed, their findings suggest that if optimal bowel and electronic cleansing are combined with state-of-the art multidetector imaging, the effects of operator dependence and interobserver variability in the interpretation of virtual colonoscopic images can be minimized. The authors report excellent interobserver agreement for polyps of 6 mm or more in diameter at all centers, and four of the six radiologists had read only 25 to 100 virtual colonoscopic scans before the study began. These findings are notable and may be critical in terms of determining whether virtual colonoscopy can successfully move beyond its current sphere in academic centers to become a feasible screening service for colorectal cancer in community-based radiology departments.

This study suggests that virtual colonoscopy can detect polyps of 6 mm or larger as accurately as conventional colonoscopy in a population with a low prevalence of colorectal neoplasia. Indeed, virtual colonoscopy allowed the detection of lesions that were missed on conventional colonoscopy. One critical issue that remains unresolved is the choice of a polyp-size threshold for virtual colonoscopy that should trigger referral for conventional colonoscopy. One model suggested by Pickhardt et al. is to offer virtual colonoscopy as an initial screening procedure and refer all patients with polyps larger than a predetermined size limit for same-day conventional colonoscopy, thereby taking advantage of the prepared colon. This approach would require that the radiologist quickly provide the endoscopist with the results of the virtual study. Obviously, this strategy would require close coordination between radiologists and endoscopists and would place a heavy demand on screening centers if large numbers of patients were to have virtual colonoscopy as the initial procedure.

The referral of all patients who were found on virtual colonoscopy to have a polyp of 10 mm or larger would probably result in the detection of nearly all cancers and eliminate the need for a large number of screening colonoscopies. However, some physicians and patients might be unwilling to wait if a smaller polyp were identified on virtual colonoscopy, for fear of delaying the removal of a small cancer. The current study does not provide any data that would support an evidence-based surveillance strategy for the follow-up of smaller polyps that are not removed. Decisions regarding the use of virtual colonoscopy as a first-line screening test will also re-

quire more information on its cost and the willingness of third-party payers to cover reimbursement.

Although almost 70 percent of the patients in the study by Pickhardt et al. found their virtual colonoscopic examination more acceptable than conventional colonoscopy, when they were asked to state their preference for a future screening test, only 50 percent chose virtual colonoscopy, as compared with 41 percent who chose conventional colonoscopy. This may reflect the reality that although many patients are attracted by a convenient, faster, less invasive, and safer virtual screening test, a substantial proportion may still opt for conventional colonoscopy because it allows suspicious lesions to be detected and removed in a single procedure.

In conclusion, the performance of virtual colonoscopy in this asymptomatic screening population is impressive, with detection rates for adenomas similar to those achieved with conventional colonoscopy. If the results of this well-designed study are reproducible on a wider scale, and if the important questions regarding the appropriate size threshold and the surveillance of smaller polyps can be resolved, then screening virtual colonoscopy is ready for prime time.

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