

## EDITORIALS

### Is Virtual Colonoscopy Ready for Widespread Application?

See articles on pages 304 and 311.

The U.S. adherence rates for colorectal cancer screening are improving but are still lower than those for prostate, breast, and cervical cancer.<sup>1,2</sup> Thus, current screening methods are onerous enough that some patients will not undergo them, and some doctors will not recommend them. All agree that new cost-effective technologies are needed, particularly ones that are less invasive or noninvasive. One method with potential is CT colonography, often called "virtual colonoscopy" (VC).

Nine years after its introduction, VC remains in pre-clinical development with regard to screening. Three multidisciplinary colorectal cancer screening guidelines have recently declined to endorse VC<sup>3-5</sup> and insurers do not pay for screening with VC. Despite this, VC is the subject of intense investigation, stimulated by genuine interest in preventing colorectal cancer deaths, higher reimbursement than double contrast barium enema (DCBE), declining interest and skill in DCBE, the financial interests of CT scanner and software makers, and a media and public that are hungry for a new approach.

As a result of media coverage that is sometimes not careful or thorough, and direct to consumer advertising by a small minority of radiologists, the public has been given a range of "spin" on VC, some of which has been inaccurate and misleading. The confusion in messages begs the question: is VC ready for use in screening or other indications, and if not, how close is it?

Colorectal cancer screening tests can be differentiated by several criteria, including effectiveness, risk, acceptability to patients, and up-front costs (cost-effectiveness is adequate for all of the current tests). A new colorectal cancer screening test does not have to outperform current screening strategies in all or even any of these categories to be accepted. A relative or particular advantage in one criterion and acceptable performance in the others could be enough to push a test to acceptance. For example, VC has considerable potential with regard to patient acceptability. In 4 of 5 studies addressing the relative acceptability of virtual colonoscopy and conventional colonoscopy in patients who had undergone both tests on the same day, virtual colonoscopy was preferred by patients in 4 studies,<sup>6-10</sup> sometimes by a wide margin. VC was

even more strongly preferred when compared to DCBE.<sup>10</sup> This difference in acceptability could outweigh reduced sensitivity or increased cost relative to conventional colonoscopy. Similarly, from the risk perspective, perforation with VC should be much lower than conventional colonoscopy.

The difficulty with VC arises in estimating its effectiveness and thus its cost-effectiveness. The literature presents a mix of successful and unsuccessful clinical trials.<sup>11</sup> Poor results in some instances are a function of radiologists who were still on their learning curves. Thus, the beautifully executed and reported study by Pineau et al.<sup>12</sup> in this issue of *GASTROENTEROLOGY* presents a level of performance in an intermediate prevalence population that, while not equal to conventional colonoscopy, would probably be considered acceptable to many (particularly if it could be reproduced in a screening population). These same investigators performed at a similar level in a larger multicenter study in which, however, the other centers generally performed poorly.<sup>13</sup> A major factor that likely contributed to the poor results achieved at other centers was that a number of the radiologists were early on their learning curves when the study started. Furthermore, in what was otherwise a very well designed trial, they were kept blinded to the correlation of individual VC and conventional colonoscopy as the study proceeded (thus learning on a case-by-case basis was prevented). Another factor in the differences between studies is interobserver variation.<sup>14</sup> Thus, radiologists differ in their cognitive ability to correctly identify subtle changes in the contour of the colon as polyps. Hardware and software<sup>15</sup> platforms are more difficult to implicate as causes of varied results, at least for large polyps.

The excellent study by Johnson et al. in this issue of *GASTROENTEROLOGY*,<sup>16</sup> now the largest study of VC in the medical literature, confirms the issue of interobserver variation and introduces another cause of poor sensitivity: low prevalence of disease. Disease prevalence is generally considered to affect predictive value but not sensitivity or specificity. However, for diagnostic tests that are more subjective, the effect of disease prevalence (or prior probability) may affect test performance or test interpretation or both. Sensitivity in colonic imaging tests is complex and operator dependent. The prevalence

of adenomas  $\geq 1$  cm in this study was 5%, similar to that in screening colonoscopy studies,<sup>17,18</sup> and much lower than the prevalence in VC studies with high sensitivity.<sup>11</sup> If the VC operator anticipates low disease prevalence, based on indication or patient demographics, then the study may be performed with less care (this effect also applies in endoscopy). For a technology highly dependent on interpretation such as VC, subtle changes in contour may be more likely to be interpreted as normal under conditions of low prevalence.

While features such as negative predictive value have been emphasized by Pineau et al.,<sup>12</sup> high negative predictive value is an expected consequence of low prevalence. Colorectal cancer is serious and I believe the primary performance feature of interest is sensitivity. The mean sensitivity for adenomas  $\geq 1$  cm of the 3 experienced radiologists in the study by Johnson et al. was 46% (range, 32%–73%).<sup>16</sup> This sensitivity is comparable to DCBE<sup>19</sup> with better acceptability but for at least a 5-fold increase in charges. Sensitivities in this range might require performance at 5-year intervals, which would negatively impact cost-effectiveness.<sup>20</sup> Also, studies of acceptability generally assume equal sensitivity of VC and conventional colonoscopy, though patients value sensitivity and would certainly be affected by knowledge of low sensitivities.

Is VC ready for widespread application? At this time, it makes perfect sense to do VC (with IV contrast) in patients with obstructing colon cancer,<sup>21</sup> if the software for doing VC is available. VC seems reasonable in the patient with incomplete colonoscopy<sup>22</sup> or who is a poor candidate for colonoscopy, although DCBE is also a good choice and costs less. High prevalence populations including bleeding indications and positive screening tests are best and most cost-effectively evaluated by conventional colonoscopy. It is too early to endorse VC for screening or surveillance, pending additional understanding gleaned from more studies in low prevalence populations. Until VC moves beyond the investigational stage for screening, it seems premature for community radiologists to invest in the software and training to perform it.

Looking forward to the next several years, VC remains promising. Fecal tagging<sup>23</sup> could dramatically enhance acceptability (but has to be proven to allow polyp detection in low prevalence populations). Perhaps computer-aided detection<sup>24</sup> can reduce interobserver variability. A biologic marker of adenomas linked to a radiographically detectable marker<sup>25</sup> would eliminate the vagaries of funny looking folds that might be sessile polyps, and very flat lesions that are invisible on VC. One or more of

these breakthroughs could prevent many colorectal cancers.

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## 6-Mercaptopurine Beats a Bum Rap

See article on page 320.

Ever since azathioprine was first proposed for the treatment of Crohn's disease in 1968 by Brian Brooke,<sup>1</sup> the distinguished British surgeon who invented the modern ileostomy, the therapy has been beset with problems.

Many of these problems are legitimate, most notably an approximate 5% frequency of adverse idiosyncratic reactions.<sup>2</sup>

On the other hand, antimetabolite treatment of Crohn's disease, with both azathioprine and 6-mercaptopurine (6-MP), has also had to endure a number of bum raps. (For those readers who are not fluent with American idioms, a "bum rap" is an unfounded or unfair allegation or indictment. One "beats" the rap if one is exonerated.)

The first of these hurdles was the misperception that azathioprine was not statistically significantly effective in treating Crohn's disease. This particular bum rap was stuck onto azathioprine principally by the National Cooperative Crohn's Disease Study,<sup>3</sup> whose deficiencies have been well aired during the past 20 years.<sup>4</sup>

Then, every clinician is familiar with patients' reluctance to take a medication they view as a cancer drug. It is helpful to reassure such patients that, although Gertrude Belle Elion and George Hitchings did indeed win the 1988 Nobel Prize for having introduced these agents

in the 1950s for the treatment of leukemia, modern use of these drugs in much lower doses has extended in the past 50 years to many other benign inflammatory diseases like rheumatoid arthritis, chronic hepatitis, and inflammatory bowel disease (IBD).

A third source of anxiety about the antimetabolites, harbored by patients and physicians alike, is that these drugs are highly toxic to bone marrow and, hence, very dangerous to use without regular monitoring of their metabolizing enzymes and end products. To be sure, the ability to measure these compounds has strengthened our use and study of these medications, but the drugs only rarely induce severe leukopenia under the usual conditions of routine clinical follow-up and regular monitoring of blood counts.<sup>5</sup>

An especially pernicious misconception about 6-MP and azathioprine is that they are contraindicated during pregnancy. It is hard to estimate the disservice that has been done by suspending their use during conception and pregnancy, when the risks to a fetus are immeasurably higher from a disease flare than from any imagined risks of the drugs.<sup>6,7</sup>

More supportable is the concern that long-term use of immunomodulators might predispose to malignancy, especially myeloproliferative diseases. This concept can no longer be dismissed as pure myth because recent studies have lent at least suggestive evidence to this effect.<sup>8,9</sup> Most clinicians, however, would agree with the observa-