

**Clinical Question:** Putting aside for the time being the controversy of whether routine use of screening colonoscopy is appropriate for an average-risk population, is CT virtual colonoscopy as accurate of a test as optical colonoscopy for detection of colorectal neoplasia in asymptomatic average-risk adults?

**Study:** Pickhardt, et.al., "Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults." *NEJM* December 4, 2003. 349:23(2191-2200).

**Background:**

- Colonoscopy is currently the gold standard test for the detection of premalignant colonic polyps, but is an invasive and uncomfortable procedure that carries an overall 0.5% complication rate (in great part due to the need for conscious sedation). The frequently quoted perforation rate for diagnostic colonoscopy is roughly 5 in 10,000. A large percentage of asymptomatic patients who are average-risk for colon cancer who undergo colonoscopy have no polyps, or only diminutive hyperplastic polyps for which polypectomy need not be undertaken. Until recently the only alternative for detection of polyps was barium enema. However, with the advent of virtual CT colonoscopy, a less invasive alternative test which does not require sedation and may be of comparable accuracy now exists. The rate of perforation in virtual colonoscopy is not known, but because air insufflation is required, it should not be assumed that the perforation rate is zero.

**Methods:**

- Asymptomatic adults age 40-79 with average risk for CRC underwent same-day virtual and optical colonoscopy. Exclusion criteria were known risk factors for CRC, history of prior screening intervention, contraindication to colonoscopy or bowel prep, and pregnancy.
- Patients underwent bowel prep (which is required for both tests) with Fleets Phospho-soda and bisacodyl, and ingested barium (to label solid stool) and Gastrografin (to opacify luminal fluid).
- Each test was performed and interpreted by a practitioner *initially* blinded to the result of the other test. The authors do not explicitly say so, but it is clear that each patient had virtual colonoscopy performed before endoscopic colonoscopy. Both tests involved insufflation of the colon (virtuals used a rectal catheter, opticals used the endoscope). Conscious sedation was used only in optical colonoscopy.
- Polyps were measured (CT: electronic calipers, endoscope: photography and calibrated linear probe). They were categorized according to size (5mm or less, 6-9mm, 10mm or more).
- "Segmental unblinding": During endoscopic colonoscopy, the result of the virtual colonoscopy was revealed to the endoscopist immediately after he or she completed evaluation of each segment of colon (starting from the cecum). If virtual colonoscopy had shown a polyp >5mm that was not apparent on endoscopy, the endoscopist was shown the CT image, then re-examined the segment of colon in search of the lesion. The authors referred to this method as an "enhanced gold standard" that they believed was *more accurate* than optical colonoscopy alone because it reassigned would-be false positives of virtual colonoscopy into the category of false negatives of optical colonoscopy.
- All polyps were sent for histology. All patients were given a questionnaire about comfort, convenience, and preferred test for the future.

**Results:**

- Of 1253 consecutively enrolled patients, 1233 underwent both tests; the other 20 were excluded because of inability to complete either endoscopy or CT, or inadequate bowel prep. Thirty-two more patients were excluded because they were later found to be higher-than-average risk.
- Table 3 summarizes the performance characteristics of virtual colonoscopy by both patient and polyp.

### **Author's conclusions:**

- "CT virtual colonoscopy...compares favorably with optical colonoscopy in terms of the detection of clinically relevant lesions."

### **Are the results of the study valid?**

1. Was there an independent, blind comparison with a reference standard?
  - Because endoscopic colonoscopy is considered the gold standard test, and the authors had a reasonable expectation of virtual colonoscopy surpassing its accuracy, they surmised that they had to invent a means of comparing virtual to endoscopic colonoscopy in a way that did not automatically count as false results for virtual colonoscopy any and all discrepancies between the two modalities. They devised the method of "segmental unblinding" to try to accomplish this. This may be creative, but it is an unproven reference standard, and in truth comparison was neither fully independent nor blind. Hence, whether or not you think virtual colonoscopy really is a more accurate test *a priori*, the authors committed a major methodological error in designing the study.
2. Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
  - The sample size, inclusion, and exclusion criteria appear appropriate to comprise the right kind of average-risk study population, but interestingly no demographic information is given in the article text or tables. It may have been helpful to know some basic information about the age, sex, and health status of the study group, as well as how many of them had a history of bowel surgery or diverticulosis.
3. Did the results of the test being evaluated influence the decision to perform the reference standard?
  - Yes and no. No, not in the way a high-probability V/Q scan may influence a physician's decision of *whether* to perform (and undertake the risk of) a pulmonary angiogram – the standard of reference was in fact employed in every case. But yes, the results of virtual colonoscopy definitely did influence *how* segmentally-unblinded endoscopic colonoscopy (the effective reference standard) assigned final judgments about what was a true and false result. There is no external proof that their "enhanced gold standard" is any more accurate than endoscopic colonoscopy, and thus no proof of validity for assuming that "positive virtual, negative endoscopic" should count as a false negative endoscopy. This is where long-term follow-up data could be very useful.
4. Were the methods for performing the test described in sufficient detail to permit replication?
  - Yes, they provide adequate details, including the bowel prep and polyp measurement techniques.
5. Overall, are the results of the study valid?
  - The study's validity rests on a key assumption: that a mucosal irregularity located on a second-look, virtual image-aided endoscopy, but unseen on initial endoscopy represents a "missed polyp." This sounds fine, but there is plenty of room for bias (like suddenly hearing the murmur after you've seen the echo report). So despite the plausibility of the study's claim, we should have serious reservations about its validity. It is provocative that one of the polyps found on unblinded endoscopy turned out to be cancer, but it would have been useful to know the histologic features of *all* the polyps discovered that way.

### **What are the results?**

6. What are the likelihood ratios for the test results?
  - Polyps 6mm or greater were of primary interest, as it is general consensus that these are of clinical importance and need removal, whereas those 5mm or less have a very high likelihood of being hyperplastic, and removal is not mandatory.

- For virtual colonoscopy:

	Disease +	Disease -
Test +	149	217
Test -	19	848

- **sensitivity** = 88.7%
- **LR+** = 4.3
- **specificity** = 79.6%
- **LR-** = 0.14

- For optical colonoscopy:

	Disease +	Disease -
Test +	155	?
Test -	13	?

- **sensitivity** = 92.3%
- **LR+** = ?
- **specificity** = ?
- **LR-** = ?

**Will the results help me in caring for my patients?**

7. Will the reproducibility of the test result and its interpretation be satisfactory in my setting?
  - Endoscopies and radiographical tests are always operator-dependent and subject to interpretation. However, the indices of interobserver variability are given and appear good.
  - We don't normally perform colonoscopies just after pumping barium and Gastrografin into patients' colons, and maybe that impaired visualization of polyps on endoscopy. At UNC, colonoscopies in patients just having gone a contrast study are generally deferred until after a second bowel preparation has been performed.
8. Are the results applicable to my patients?
  - Yes in general; the patient population tested is average-risk, much like those I screen for colon cancer in my practice. Many of my patients would be interested in a less invasive and risky test that is still accurate at finding polyps; however, virtual colonoscopy actually rated more poorly in terms of comfort.
9. Will patients be better off as a result of the test?
  - There are no direct studies indicating that *any* screening colonoscopy alone, whether virtual or endoscopic, reduces colorectal cancer-related mortality. Those who believe screening colonoscopy is beneficial do so based on indirect evidence from FOBT and sigmoidoscopy trials. It is tempting to believe that patients overall would be better off realizing the benefits of colonoscopy screening without risks of perforation and side effects of conscious sedation, but this study does not directly answer that question.