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January 24, 2008

Denise C. Santoyo
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Submitted via e-mail to: shtap@hca.wa.gov

Dear Ms. Santoyo:

On behalf of the American College of Gastroenterology, including some 200 members in Washington State, we would once again like to provide expert commentary to aid in your agency's assessment of Virtual Colonoscopy/Computed Tomographic Colonography (CTC). We provided preliminary guidance on CTC to your agency in the first-round of information gathering as well as on the questions posed in December. At this time, we would like to comment on the Health Technology Assessment (HTA) conducted by the Institute for Clinical and Economic Review dated January 11, 2008. While it is an impressive study, we have several concerns about its findings, and as a leading specialty society the College believes that clinical evidence must inform reimbursement and technology assessment decisions.

Colorectal Cancer Screening and Polyp Size

As we commented previously, small polyps cannot be ignored. We are concerned that this evidence review chose to ignore the performance of CTC for polyps less than or equal to 5 millimeters. There is ample evidence to show the clinical significance of such polyps.

First, the National Polyp Study has shown that three adenomas of any size is the most consistent predictor of an advance adenoma, and 80% of all adenomas are < 6mm. Furthermore, in a recent analysis of the extensive colonoscopy database at Indiana University by Dr. Doug Rex, 30% of all patients with high risk adenomas as defined by post-polypectomy surveillance were patients with 3 adenomas less than 6 mm in size and no polyp of any histology 6 mm or larger. Hence it is problematic to dismiss polyps based on size or infer that polyps < 6mm are inconsequential.

Second, a recent study (Butterfly et al Clin Gastroenterol Hepatol 2006;4(3): 343-48) emphasized the prevalence of clinically important histology in small adenomas. Data were reviewed retrospectively from 3,291 colonoscopies performed on asymptomatic patients found to have an adenoma on screening with flexible sigmoidoscopy a few weeks before the colonoscopy or who had a family history of colorectal cancer. All polyps were excised endoscopically and sent for pathology testing. Specimens with advanced histology were confirmed by a second reading. Of the 3,291 colonoscopies performed, 1,235 yielded a total of 1,933 small or diminutive adenomatous polyps.

Advanced histology including carcinoma was found in 10.1% of small (5–10 mm) adenomas and in 1.7% of diminutive adenomas (≤4 mm). Carcinoma was found in .9% of small adenomas, and 0% of diminutive adenomas.

In addition to ignoring small polyps generally, the report also specifically fails to address the implications of dismissing small polyps found by CTC. A recent decision analysis (Hur et al. Clin Gastroenterol Hepatol 2007; 5(2): 237-244) addressed this issue. The authors reported that if CTC is used for colorectal cancer screening, the majority of polypoid lesions identified will be less than 10 mm in size. Decision-analytic techniques were used to compare the outcomes of 2 management strategies for smaller (6–9 mm) polyps discovered by CTC. Hypothetic average-risk patients who had undergone a CTC examination and found to have a small (6–9 mm) polyp were simulated to either: (1) undergo immediate colonoscopy for polypectomy (COLO), or (2) wait 3 years for a repeat CTC examination (WAIT). A Markov model was constructed to analyze outcomes including the number of deaths and cancers after a 3-year follow-up period or time horizon. Values for the model parameters were derived from the published literature and from Surveillance Epidemiology and End Results data, and an extensive sensitivity analysis was performed. The colonoscopy strategy resulted in 14 total deaths per 100,000 patients compared with 79 total deaths in the WAIT strategy, for a difference of 65 deaths. The colonoscopy strategy resulted in 39 cancers per 100,000 patients vs. 773 in the WAIT strategy, for a difference of 734 cancers. Sensitivity analysis found that model findings were robust and only sensitive at extreme parameter values. The study concluded that managing smaller polyps detected on a screening CTC with another CTC examination 3 years later likely will result in more deaths and cancers than immediate colonoscopy and polypectomy.

CTC Complications

We would like to alert you to some inaccuracies and incomplete analyses in the discussion of potential harms of CTC. For instance, the current draft states, that CTC has “a far lower rate of complications than colonoscopy, due to absence of risk of perforation (0 per thousand vs. 0.7 per thousand.)” In fact there are two extremely large studies involving CTC that cite a perforation rate comparable to optical colonoscopy (Sosna J et al. Colonic perforation at CT colonography: Assessment of risk in a multicenter large cohort. Radiology 2006 May; 239:457-63.

Burling D et al. Potentially serious adverse events at CT colonography in symptomatic patients: National survey of the United Kingdom. Radiology 2006 May; 239:464-71)

Recognizably also the number of complications for colonoscopy encompasses all diagnostic and therapeutic procedures (polypectomy), hence these complications need to be put in perspective also against alternative intervention (surgery) vs. no intervention as well as distinguish between screening and diagnostic colonoscopy. In the first study, researchers reviewed data from 11,870 CTC studies performed at 11 centers in Israel during a two-year period. These studies represented more than 95% of all CTC studies performed in Israel during this interval. Seven perforations occurred, yielding a rate of 1 in 1700 (0.06%). Five perforations occurred in the sigmoid colon and two in the rectum. Four patients required surgical treatment.

In the second study, researchers interviewed the lead gastrointestinal radiologists at 50 centers in the UK to determine the number of CTCs ever performed and the number of perforations. Of 17,067 patients who underwent CTC, 9 had perforations (1 in 1900 or 0.05%). Overall, the perforation rate among symptomatic patients in these studies ranged from 0.03% (1 in 3400 patients) to 0.06% (1 in 1700 patients). These rates are much higher than those seen with barium enema and, for many individual endoscopists, exceed the rates of diagnostic perforation during conventional colonoscopy.

Patient Acceptance

The executive summary states that “...among patients who experienced both CTC and colonoscopy, a small majority preferred CT colonoscopy.” This statement may ignore key subpopulations. For

instance, there is a recent report suggesting a bias a minorities AGAINST CTC compared to colonoscopy. This might be important to acknowledge given the disparity of CRC screening in the US for minorities. (Roshini et al. Clin Gastroenterol Hepatol 2007; Aug 3). This is important as racial/ethnic minorities are less likely to undergo CRC screening than whites. Racial/ethnic minorities were significantly less likely than whites to prefer CTC over OC (whites, 65.7%; blacks, 45.1%; Hispanics, 35.8%; and other, 35.7%; $P < .001$). Racial/ethnic minorities were less satisfied with CTC (whites, 8.4 +/- 1.7; blacks, 7.8 +/- 1.7; Hispanics, 7.4 +/- 1.8; and other, 7.5 +/- 2.1; $P = .001$) and were significantly less willing to undergo CTC again in the future (whites, 95.5%; blacks, 80.3%; Hispanics, 84.9%; and other, 85.7%; $P = .006$). Compared with white patients, colonoscopy was better tolerated and preferred over CTC for evaluation of the colon among racial/ethnic minorities. Given the serious challenges we face in this country with healthcare disparities including in access to CRC screening, this data should not be ignored.

New Methods of Bowel Preparation

The discussion (see page 9 of the report) states “on the horizon there is new method of bowel prep for CTC and this is a non-cathartic, and if this method is demonstrated to provide the same sensitivity/specificity as current CTC, patient acceptance of CTC is likely to be much higher than for colonoscopy. Our clinical experts estimated that evidence on the performance of non-cathartic prep would be available within the next 9-12 months.” We would suggest that, from an evidence-based review based on published data, that this assertion is conjectural and inappropriate. A non-cathartic approach to CTC (Mayo Clin Proc 2007;82:666-71) suggested that preparation for CTC was in fact necessary for optimal utilization – if CTC was to be done. The absence of a cathartic prep would preclude same day colonoscopy. The greatest aversion for a cathartic prep was from prior exposure. Most importantly-the majority of data and all the data on screening with CTC has been with a cathartic based preparation.

Economic Modeling

The College is concerned that, as the report states, “The economic model does not explicitly simulate hyperplastic polyps.” (page 10) The assumption for that model was based on size and not histology. Dismissal of polyps <6mm as hyperplastic is conjectural as to the actual histology and not an accurate assumption.

CTC is an expensive examination, being at least five times more expensive than the current radiographic imaging test for colon polyps, double contrast barium enema.

30% or more of patients undergoing CT colonography in many centers might be sent for conventional colonoscopy for false positives. These specificities are indeed lower than what has been traditionally reported for double contrast barium enema. In one large study of CT colonography, 197 of 300 patients had a true or false positive polyp (Yee, Radiology 2001;219:685-92). The recent abstracted report from the ACRIN trial cites a specificity of 86% for reportable polyps. This means that over a ten year period, at least 42% of patients would be referred for a colonoscopy. This was not the assumption used in the present cost modeling for discussion of cost effectiveness. Additionally, earlier follow-up for smaller polyps was not built into the logic of the assumptions; hence these cost modeling data are very misleading.

Radiation Risk

The College is troubled that the discussion of radiation exposure and future cancer risk that begins on page 34 of the report inappropriately diminishes the risk of radiation exposure associated with abdominal CT imaging. Conservative estimates are that more than 60 million CT examinations were done in 2002 in the USA, representing an estimated 70% of all medical X-ray exposure. (OW Linton and FA Mettler Jr,

National conference on dose reduction in CT, with an emphasis on pediatric patients, *AJR Am J Roentgenol* 181 (2003), pp. 321–329) Although it is a challenge to define precise risk estimates related to low doses of radiation exposure, the ionizing radiation exposure from a single abdominal or chest CT may be associated with elevated risk for DNA damage and cancer formation (M Lobrich, N Rief and M Kuhne et al., In vivo formation and repair of DNA double-strand breaks after computed tomography examinations, *Proc Natl Acad Sci USA* 102 (2005), pp. 8984–8989.) The seventh National Academy of Science report on Biological Effects of Ionizing Radiation (BEIR) is the most recent update from a respected organization. (Committee to Assess the Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII: health risks from exposure to low levels of ionizing radiation (<http://www.nap.edu/reportbrief/11340/11340rb.pdf>) BEIR VII indicated that a single population dose of 10 mSv is associated with a lifetime attributable risk for developing a solid cancer or leukemia of 1 in 1000. The overall risk for developing a solid cancer or leukemia from all causes would be 42 in 100.

The radiosensitive tissues are predominantly within the field of view of common chest, abdominal, and pelvic CT scans: the typical abdominal examination dose is between 10 and 20 mSv. Unfortunately many patients are exposed to multiple examinations that increase cumulative dosing. A recent report focused on the effects of multiple exposures to ionizing radiation during CT. They found that a subset of patients with renal colic commonly had total exposure rates between 19.5 and 153.7 mSv (SI Katz, S Saluja, JA Brink and HP Forman, Radiation dose associated with unenhanced CT for suspected renal colic: impact of repetitive studies, *AJR Am J Roentgenol* 186 (2006), pp. 1120–1124)

Radiation effects may not manifest until 5–20 years after the scan, and causal relations are unapparent on an individual basis.

The US Food and Drug Administration has listed medical X-rays as a known carcinogen. It may be necessary for governments to place guidelines on acceptable maximum doses and indications for CT. For instance, questionable practices such as whole-body CT screening examinations that expose normal individuals to known risks with unknown benefits might need to be restricted.

Cross-sectional imaging has revolutionized diagnosis and medical practice in the past 30 years. Clinicians, as patients' advocates, are obliged to understand and explain the risks associated with CT radiation, and to provide state-of-the-art dose-reduction techniques,

X-rays used in medical diagnostic procedures is the largest man-made source of radiation exposure to the population, contributing with some 14% of the total annual exposure from all sources. Ionizing radiation from diagnostic procedures has been postulated to cause several hundred cases of cancer per year in the UK (AB de Gonzales and S Darby, Risk of cancer from diagnostic x-rays: estimates for the UK and 14 other countries, *Lancet* 363 (2004), pp. 345–351)

It is, however, reasonable to assume that many health professionals underestimate the potential hazard of ionizing radiation in common diagnostic procedures. The authors should also discuss the implication of obesity on dosimetry requirements for these exams. Obesity (60 million US; 30% of population) increases the dosimetry for accurate CT imaging, approximately by a factor of 2. Hence the impact of repeated higher dose exposures for these patients over time may be even more important- in a patient group that already has a higher associated risk for many intra-abdominal cancers.

Miscellaneous Comments

The report's introduction refers to CTC as "non-invasive," which is a suboptimal choice of phraseology as CTC requires prep, rectal tube insertions/air insufflations, radiation exposure and in many studies the use of intravenous medicine.

With regard to the report's methodology which on page 29 states that the review identified four components of CTC "using the best technology and performance standards," we would point out that the comparison of optical colonoscopy is not held to the same standards, and in the real world, it is likely that CTC would not always be done consistently with these criteria.

We appreciate the agency's collaborative and transparent approach to technology assessment thus far on CTC and appreciate the opportunity to comment on the ICER review. Please don't hesitate to contact me or Julie Cantor-Weinberg, the ACG's Vice President of Public Policy, if we can clarify any responses or provide you with any additional information.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Amy Foxx-Orenstein". The signature is fluid and cursive, with the first name "Amy" being the most prominent.

Amy Foxx-Orenstein, D.O, FACP
President