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January 4, 2008

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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, I would like to provide our proposed answers to your draft key questions issued on December 21, 2007 as part of a technology 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 a leading physician-organization dedicated to quality colorectal screening, we are pleased to have the opportunity to continue to serve as a resource to your decision-making.

The American College of Gastroenterology is a physician organization representing gastroenterologists and other gastrointestinal specialists. Founded in 1932, the College currently numbers more than 10,000 physicians among its membership of health care providers of gastroenterology specialty care. Although the vast majority of these physicians are gastroenterologists, the College's membership also includes surgeons, pathologists, hepatologists, and other specialists in various aspects of the overall treatment of digestive diseases and conditions. The College has chosen to focus its activities on clinical gastroenterology – the issues confronting the gastrointestinal specialist in treatment of patients. The primary activities of the College have been, and continue to be, educational efforts directed at promoting and optimizing quality care.

Attached you will find our answers to your five draft questions.

We look forward to continuing to work with you and the Health Care Authority as the agency develops its technology assessment on HTA. 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,

Amy Foxx-Orenstein, D.O, FACG
President

**AMERICAN COLLEGE OF GASTROENTEROLOGY RESPONSES TO
DRAFT KEY QUESTIONS ON VIRTUAL COLONOSCOPY OR
COMPUTED TOMOGRAPHIC COLONOGRAPHY (CTC)**

Question 1:

What is the evidence to describe sensitivity, specificity, and other key test characteristics of CTC compared primarily to optical colonoscopy but also in the context of the test characteristics of accepted modalities of colorectal cancer screening?

The forthcoming National CT Colonography Trial (ACRIN 6664), a study funded by the National Institutes of Health (NIH) and performed on 2,531 participants in 15 U.S. centers has not yet been released in the peer review literature. The overall performance from the data for ACRIN as presented in abstract was acceptable with regard to sensitivity, but specificity and positive predictive value were very disappointing. The specificity for polyps greater than 1 cm in size was 86%, and the positive predictive value was 25%. Those are major problems with CTC performance that should be discussed with regard to potential harms and benefits.

At those levels, CTC every five years will require significant additional optical colonoscopy. After 10 years and three cycles, 42% of the population will be colonoscoped for false positive large polyp findings, in addition to those that are scoped for true positive findings and false positive polyps smaller than 1 cm, increasing costs significantly.

Positive predictive values of 25% in clinical practice will be very problematic. Colonoscopies will be prolonged, and it is likely that colonoscopies that are negative in a patient with a positive CT colonography will lead to another CT colonography within a year. Substantial percentages of the population will therefore undergo two CTCs to prove that they did not have a polyp to begin with.

Question 2:

What is the evidence relating to test characteristics of CTC variance according to the type of scanning machine and software, bowel preparation, reader training, and other operational factors?

The data for variability with CTC interpretation has been quite alarming. The study by Johnson et al was a single center study performed at the Mayo Clinic Rochester. Among 703 patients, the reported sensitivity among three experienced examiners for polyps >9 mm was 32%, 35%, and 73%, with a mean sensitivity of 46% (Johnson, Gastroenterology 2003;125:311-9). The Cotton study was a nine center study in the United States involving 615 patients, with a primary end point of finding patients with polyps ≥ 6 mm in size and reported an overall sensitivity for this end point of 39%, with a sensitivity of 55% for identifying patients with polyps ≥ 1 cm in size (Cotton, JAMA 2004;291:1713-9).

Sensitivities of CT colonography for polyps in the 6-9 range have often been quite low and have been 16%, 22%, 43%, 47%, and 39% in five studies (Miao, Gut 2000;47:832-7; Mendelson, MJA 2000;173:472-5; Rex, Gastrointest Endosc 1999;50:309-13; Fletcher, Radiology 2000;216:704-11; Kay, Endoscopy 2000;32:226-32).

Question 3:

What is the evidence about patient attitudes and acceptance of screening between CTC and colonoscopy?

Comparative studies of CTC and colonoscopy have suggested a preference for optical colonoscopy.

Comparison of Patient Experience for Three Colon Imaging Procedures

	Air Contrast Barium Enema	Colonoscopy	Computed Tomographic Colonography	P Value
Painful	2.90 (3)	3.7 (4)	3.02 (3)	.0001
Worried about the procedure	3.06 (3) [†]	3.22 (3)	3.45 (4)	.0001
Difficult to follow directions	4.22 (4)	4.22 (4)	4.25 (4)	.94
Preparations unpleasant	2.77 (3)	2.67 (2)	2.69 (2)	.07
Procedure uncomfortable	2.26 (2) [‡]	3.46 (4)	2.62 (2)	.0001
Embarrassed	3.74 (4) [‡]	4.06 (4)	3.95 (4)	.0001
Respect	1.59 (1)	1.61 (1)	1.54 (1)	.53
Willingness to have test again	2.08 (2) [‡]	1.78 (2)	1.90 (2)	.0001
Worn out from procedure	3.22 (3) [‡]	3.03 (3)	3.57 (4)	.0001
Procedure inconvenient	3.08 (3) [‡]	3.30 (3)	3.33 (3)	.0001
Satisfied	2.11 (2) [‡]	1.81 (2)	1.94 (2)	.0001

Median numbers are given in parentheses. Because of the design of the questionnaire, the lower the number, the greater the agreement (see supplemental Web material for the questionnaire). (Source: Am J Med 2006;119(9):791-99.)

Colonoscopy is significantly different than barium enema and virtual colonoscopy (Wilcoxon).

[†] Air contrast barium enema is significantly different than colonoscopy and virtual colonoscopy.

Additionally, there is recent evidence reporting on a racial preference for optical colonoscopy over CTC (Clin Gastroenterol Hepatol. 2007 Nov;5(11):1306-12). This study reported that 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, OC was better tolerated and is preferred over CTC for evaluation of the colon among racial/ethnic minorities. These findings suggest that CTC is unlikely to overcome racial/ethnic disparities in CRC screening.

There is some data to suggest that patients prefer optical colonoscopy over CTC since with proper anesthesia it is “painless” and only requires one procedure whereas if there is a positive or inconclusive CTC, optical colonoscopy with additional bowel preparation would be required.

Question 4:

What is the evidence about patient characteristics that influence benefits and harms of CTC over usual cancer screening?

Radiologists are currently discussing a 1 cm cutoff size for CTC, in which polyps that are detected that are less than that in size would either be ignored or followed up in a few years by repeat CTC. However, there is no evidence to demonstrate the safety of this approach. Overall, the literature suggests that polyps in the 6-9 mm range have an approximately 1% prevalence of invasive cancer, and it is unlikely that patients or primary care physicians will accept leaving these polyps in place for 10 year intervals. Ignoring polyps less than 1 cm in size is an approach that has not previously been used in clinical practice and has never been the approach to polyps detected during barium enema.

Furthermore, there is a firm consensus that larger (greater than or equal to 10 mm) colonic polyps should be removed; however, the importance of removing smaller polyps (less than 10 mm) is more controversial. In a recent analysis by Hur et al (Clin Gastroenterol Hepatol 2007; 5(2): 237-244) the authors addressed the proposed approach by CTC radiologists as to “offer” colonoscopy for polyps 6-9 mm and to not report polyps less than 6mm. Closer interval surveillance would be part of this recommendation as well. 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 three-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 COLO 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 COLO 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 authors conclude that managing smaller polyps detected on a screening CTC with another CTC examination three years later likely will result in more deaths and cancers than immediate

colonoscopy and polypectomy. Given the recent robust data from CDC suggesting a decrease in CRC and related death, we believe that a test that ignores or minimizes importance of lesions less than 1cm poses a significant threat to the value of CRC screening.

The CTC related radiation risks are of significant concern. Most of the quantitative information on radiation risks and radiation-induced cancers comes from studies of survivors of the atomic bombing in Japan in 1945. This cohort of patients has been studied over time. Of note, there was a significant increase in the overall risk of cancer in these patients/survivors who received "low dose" radiation, ranging from 5-150 mSv. The mean dose for this group was approximately 40 mSv, which approximates the relevant organ dose exposure from a typical CT study in which 2-3 scans are done in a patient. The concerns are further corroborated by a recent study involving over 400,000 radiation workers in the nuclear industry. This study also reported a significant association between radiation dose and mortality from cancer. The range of exposure was between 5 and 150 mSv. These risks were quantitatively consistent with those of the atomic bomb survivors. Results of prospective studies for patients who undergo CT scanning will not be available for a long time, but it is possible to estimate the risks of exposure by estimating the organ radiation dose exposure and applying the organ-specific cancer incidence or mortality data derived from the studies of the atomic bomb survivors.

Brenner and Hall (*N Engl J Med.* 2007;357:2277-2284) estimated the lifetime risk of death from cancer that was attributable to a single "generic" CT scan of the head or abdomen. The risks varied depending on the age of patient at exposure and the organ-specific dose exposure.

Study Type	Relevant Organ	Relevant Organ dose (mGy or mSV)
Posterior-anterior chest x-ray	Lung	0.01
Lateral chest x-ray	Lung	0.15
Screening mammogram	Breast	3.00
Abdominal CT scan (adult)	Stomach	10.00
Abdominal CT scan (neonate)	Stomach	20.00
Barium enema	Colon	15.00

Even though the doses are higher for the head CT scan, the risks are higher for abdominal scans because the digestive organs are more sensitive than the brain to development of radiation-induced cancer. Extrapolating from the data provided, the risk of cancer-related death associated with one abdominal CT scan is 0.06% for a patient exposed at 25 years of age and 0.02% for a patient exposed at age 50. This risk is striking and apparent when looking at the lifetime radiation risk of two of the most common radiogenic cancers, namely lung and colon cancer. For exposure to as little as 10 mSv at 25 years of age, the risk of death from lung or colon cancer is .025% and 0.0125%, respectively. For a patient exposed at 50 years of age, these associated risks are 0.017% and 0.010% for lung or colon cancer, respectively.

If indeed clinicians are not well versed in radiation risks associated with CT examination, it may not be surprising that these risks might not be explained clearly to patients before obtaining consent for an examination. By comparison, the estimated risk of serious complications and death from receiving iodinated intravenous CT contrast is approximately 1 in 400 000, which is

lower than the lifetime attributable risk from a single 10 mSv dose of radiation. Yet considerable attention is given to contrast risk during the consent process. This difference may be accounted for on the basis of a clear causal relation: contrast is injected and the patient immediately develops symptoms. Radiation effects, however, may not manifest until 5–20 years after the scan, and causal relations are unapparent on an individual basis.

Question 5:

What is the evidence about the cost impact of CTC?

With the frequency of repeat CTC there is considerable concern over the cost effectiveness of this approach. In the study by Kim (N Engl J Med 2007; 357: 1403-1412) further testing was recommended in 7.7% of studies for indeterminate "probably unimportant or incompletely characterized lesions. The cost impact with further testing for incidental findings, direct risks associated with these tests- possible biopsies, indirect costs (e.g. patient related stress, work, quality of life), and extended risks of further radiation testing and long term related cost consequences of radiation related complications raise serious concerns.

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 (DCBE).

30% or more of patients undergoing CTC in many centers might be sent for conventional (optical) colonoscopy for false positives. These specificities are indeed lower than what has been traditionally reported for DCBE. In one large study of CTC, 197 of 300 patients had a true or false positive polyp (Yee, Radiology 2001;219:685-92).

Currently, there are no guidelines for clinicians in practice to utilize to decide which polyps detected in CTC should be referred for colonoscopy. There are also no guidelines for what interval should be used for repeat examinations in patients who have negative CTCs, or who have CTC that demonstrate polyps but the polyps are considered to be of a size that does not warrant colonoscopy and polypectomy at present. Further, the cost-effectiveness of CTC has not been established.

For example, Aetna recently issued a national non-coverage decision for CTC as a screening tool with very narrowly tailored exceptions. In its review of the evidence, the insurance giant stated, "More clinical trials need to be conducted to assess the cost-effectiveness and efficacy of virtual colonoscopy in comparison with conventional colonoscopy and sigmoidoscopy. The current cost of virtual colonoscopy probably prohibits its use as a screening tool." (See http://www.aetna.com/cpb/medical/data/500_599/0535.html.)