January 30, 2019

Submitted Electronically

United States Preventive Services Task Force
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

RE: United States Preventative Services Task Force Draft Research Plan for Colorectal Cancer Screening

Dear Task Force Members:

The American College of Radiology (ACR), representing more than 38,000 diagnostic radiologists, interventional radiologists, radiation oncologists, nuclear medicine physicians and medical physicists, appreciates the opportunity to comment on the United States Preventative Services Task Force's (USPSTF) draft research plan for colorectal cancer screening. The ACR feels strongly that current evidence on the risks and benefits of Computed Tomography colonography (CTC) continue to show that CTC is proven to be an effective tool for screening of asymptomatic patients for colorectal cancer. Significant peer-reviewed evidence on the efficacy of CT colonography has been and continues to be published on a regular basis.

CTC is a valuable screening technology that can advance the goal of increasing colorectal cancer screening rates and reduce the mortality rate in colorectal cancer patients. There are more than 145,000 Americans diagnosed with colorectal cancer every year, and over 50,000 die because of late detection. Colorectal cancer is the third most common cancer diagnosed among men and women in the United States and the second overall leading cause of cancer death considering men and women together, despite having a 90 percent cure rate when detected early.

Providing patients a variety of effective screening tools for colorectal cancer encourages early detection in the fight against this deadly disease and helps save lives as well as closing the gap in colorectal screening rates between whites and minority populations. This letter outlines the publication of dramatic new evidence of the value of CTC, the increase in screening that will save lives, and a reduction in the racial/ethnic disparities that plague colon cancer screening adoption. The issues of extracolonic findings and radiation dose exposure are also addressed.

Important clinical evidence

In 2018, the American Cancer Society published their updated guidelines for colorectal cancer screening, which concluded that adults aged 45 years and older with an average risk of colorectal cancer should undergo regular screening using one of a variety of available screening options, including CTC every 5 years[1].

[1] Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68:250-281.

In 2008, the National CTC Trial supported by the National Cancer Institute and administered by the ACR Imaging Network (ACRIN) sought to evaluate the accuracy of CTC in a screening population using optical colonoscopy as the gold standard[2]. Fifteen different medical centers participated nationally, including both private practice and academic centers. The trial recruited 2,600 asymptomatic individuals that were prescheduled for screening colonoscopy. A full bowel prep, stool and fluid tagging, as well as state of the art CT scanners and techniques were utilized. Trained and tested radiologists reported all lesions 5 mm or larger. Complete data were available for 2,531 (97 percent) participants. For adenomas 1 cm or larger the per patient estimates for sensitivity, specificity, positive and negative predictive values as well as the area under the receiver operating characteristic curve were 0.90 ±0.03, 0.86 ± 0.02, 0.23 ± 0.02, 0.99 ±<0.01, and 0.89 ± 0.02, respectively. Per-patient sensitivity estimates ranged from 67 to 100 percent (7 of 15 readers detected all large lesions). Per-polyp sensitivity for large neoplasia was 0.84 ± 0.04; indicating 16 percent of large lesions detected on colonoscopy were not seen on CTC. Per-patient sensitivity estimates in detecting adenomas ≥ 6 mm was 0.78. CTC screening identified 90 percent of asymptomatic patients with neoplasia ≥ 10 mm in diameter. These findings augment previously published data regarding the role of CTC in average-risk CRC screening.

Increased Colorectal Cancer Screening Rates

A variety of literature shows an increase in colorectal cancer screening rates with the introduction of CTC as a covered screening option. In both the University of Wisconsin and Colon Health Initiative (CHI) experiences, colorectal cancer screening adherence improves with the implementation of CTC[3,4]. As opposed to substituting one exam for the other, the addition of CTC to the current menu of CRC screening options appears to increase overall rates. At the former National Naval Medical Center (now Walter Reed National Military Medical Center), since 2005, colorectal screening has increased by 33 percent with more than 70 percent of beneficiaries compliant with CRC recommendations following the integration of CTC screening with the existing colonoscopic program. Another study demonstrated improved Healthcare Effectiveness Data and Information Set (HEDIS) compliance, up to 84% for colorectal cancer screening with the inclusion of CTC[5].

Of note, on October 2016, the National Committee for Quality Assurance (NCQA) released the Healthcare Effectiveness Data and Information Set (HEDIS) 2017 Technical Specifications Update, which included the addition of CT colonography to the colorectal cancer screening measure[6].

A study of 250 average-risk patients undergoing colorectal cancer screening found that the most common reasons for choosing CTC included convenience (33.6%), recommendation by a

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[2] Johnson CD, Chen MH, et al. The national CT colonography trial: multicenter assessment of accuracy for detection of large adenomas and cancers. N Engl J Med 2008; 359:1207-1217.
[3] Schwartz DC, Dasher KJ, Said A et al. Impact of a CT colonography screening program on endoscopic colonoscopy in clinical practice. Am J Gastroenterol 2008;103:346-351
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[6] NCQA Releases 2017 CRC HEDIS Measure. Retrieved from: http://nccrt.org/ncqa-releases-2017-crc-hedis-measure/. Accessed on January 30, 2019.

referring provider (13.2%), and safety (10.8%). If CTC were not an available option, 36% of the 250 enrolled patients would not have undergone colorectal cancer screening. Among the 57 patients who underwent both procedures, 95% preferred CTC[7]. In a study of 1,417 adults undergoing CTC screening in three different settings including a community practice, academic center and military medical center the top reason for choosing CTC was avoidance of the risks and expense of anesthesia. Of 441 respondents who experienced both CTC and colonoscopy, 77.1% preferred CTC and 13.8% preferred colonoscopy. Of all patients, 19.6% indicated that they may not have undergone colonoscopy screening if CTC were not available. Of all respondents, 93% indicated that they would choose CTC for their next screening[8].

Reduced Racial/Ethnic Disparities in Screening

A study evaluating preferences for colorectal cancer screening among racially and ethnically diverse patients found that ratings of CT were significantly higher than ratings of colonoscopy, sigmoidoscopy, and fecal occult blood testing in African American and Hispanic patients[9].

A study evaluating the performance of CTC in a screening cohort of 2490 African Americans found that CTC was an effective screening modality with a per-patient CTC positive rate of 9.8% for polyps measuring 6 to 9 mm, 5.4% for polyps measuring 10 to 29 mm, and 1.3% for masses ≥ 30 mm. The referral rate to optical colonoscopy was 13.9%[10].

Other Issues: Extracolonic findings at CTC

Extracolonic findings (ECF) have led to debate and misunderstanding in terms of their incidence and impact in screening cohorts at CT colonography. Although high rates have been reported in symptomatic patients, including patients with colon cancer and metastatic disease[11,12,13], low rates of clinically significant ECF of 4.5 to 16% has been reported in large screening cohorts[14]. Equally as important is the actual rate of additional imaging which occurs, which demonstrates the true impact of these findings.

Since the USPSTF guidelines were released in 2016, a large meta-analysis of ECF in CT colonography was published including 44 studies of both screening and symptomatic cohorts

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[7] Moawad FJ, Maydonovitch CL, Cullen PA, et al. CT colonography may improve colorectal cancer screening compliance. AJR 2010;195:1118-1123.

[8] Pooler BD, Baumel MJ, Cash BD, et al. Screening CT colonography: multicenter survey of patient experience, preference, and potential impact on adherence. AJR 2012;198:1361-1366.

[9] Hawley ST, Volk RJ, Krishnamurthy P, et al. Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients. Med Care 2008;46:S10-6.

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[11] Kahn KY, Xiong T, McCafferty I et al. Frequency and impact of extracolonic findings detected at computed tomography in a symptomatic population. British J of Surgery 2007;94:355-361.

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[13] Hellstrom M, Svensson MH, and Lasson A. Extracolonic and incidental findings on CT colonography (virtual colonoscopy). AJR 2004; 182:631-638.

[14] Pickhardt PJ, Choi JR, Hwang I, et al. Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults. N Engl J Med 2003;349:2191-2200.

(49,676 patients) from 1994 to 2017[15]. The pooled rate of potentially important findings was 4.9% (95% CI 3.7-6.4%). Importantly, this estimate declined over time, averaging 9% decrease per year since 2006 and was significantly lower with the use of the C-RADS reporting system for CT colonography. The overall pooled rates of recommended work up were 8.2% for all extra-colonic findings and 4.0% for potentially important ECF.

Also recently published since the 2016 USPSTF guidelines, a screening cohort of 2,490 African Americans (85% male) reported a rate of 4% for E4 (potentially important) findings in patients 50 to 80 years old[16]. Another new series of over 3,000 low risk but symptomatic patients was published in 2017, with a rate of 8.4% for E3 (indeterminate but may require additional imaging) and 2.0% for E4 ECF findings[17]. These new large series continue to demonstrate the low rates of clinically significant ECF at CTC.

A study comparing ECF rates in screening and diagnostic CTC patient cohorts was performed and found low rates in both. 68% (262/388) underwent screening and 32% (126/388) diagnostic CTC. 7.2% had extracolonic findings considered potentially significant (E4), 4.4% had indeterminate but likely unimportant findings (E3), and 88.4% had normal or unimportant findings (E1 or E2). 4.6% of patients with E3/E4 findings in the screening cohort demonstrated clinically significant outcomes, compared with 4.0% in the diagnostic cohort, including a total of three extracolonic malignancies (0.8%) and three abdominal aortic aneurysms (0.8%)[18].The distribution of extracolonic findings and clinical outcomes were not statistically significantly different between screening and diagnostic CTC populations.

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[15] Pickhardt PJ, Correlate L, Morra L, Regge D, Hassan C. Extra-colonic findings at CT colonography: systematic review and meta-analysis. AJR 2018;211:25-39.

[16] Moreno CC, Fibus TF, Krupinski EA, Kim DH, Pickhardt PJ. Addressing racial disparity in colorectal cancer screening with CT colonography: experience in an African-American Cohort. Clin Colorectal Cancer. 2018 Jun;17(2):e363-e367. doi: 10.1016/j.clcc.2018.02.007. Epub 2018 Feb 20.

[17] Netz FRS, Pickardt PJ, Heijnen MLG, Simons PCD. Detections of potentially relevant extra-colonic findings at CT colonography in a low risk symptomatic patient population. Abdom Radiol 2017;42:2799-2806).

[18] Taya M, McHargue C, Ricci ZJ, Flusberg M, Weinstein S, Yee J. Comparison of extracolonic findings and clinical outcomes in a screening and diagnostic CT colonography population. Abdom Radiol. 2018 Sep 12. doi: 10.1007/s00261-018-1753-3. [Epub ahead of print]

In addition to the use of the C-RADS reporting structure for quality assurance, significant efforts by the ACR Incidental Findings Committee has led to numerous guidelines regarding standardization and optimizing the reporting of incidental findings in radiology[19,20,21,22,23.]

One issue not often addressed, but which should be included in discussions on the efficacy of CTC is the benefits of extracolonic diagnoses. There are serious findings that could be discovered to the patient's benefit, including extracolonic cancers and abdominal aortic aneurysms (AAA). Veerappan et al. reported that the prevalence of EC cancers was equivalent to unsuspected colorectal cancers in their large screening series (n=2,277)[24]. Similar results were seen in a larger screening cohort of over 10,000 patients where the extracolonic cancer prevalence was 0.35% whereas the colorectal cancer prevalence was 0.21%[25]. The AAA prevalence has been reported at 0.5% (up to 1% in screening males)[26]. The benefits of screening for AAA have already been established for older males—and these can be accurately detected at CTC due to its cross-sectional nature. Hassan et al. modeled the impact of incorporating the impact of extracolonic neoplasms and AAA into CTC screening[27]. This group demonstrated that there were substantial gains in life years by CTC screening because of the coincident ability of CTC to detect AAA in addition to detecting colorectal high risk lesions.

Radiation Dose

Comparison of the radiation exposure of CTC to radiation exposures from naturally occurring sources is helpful in placing the low doses of radiation from CTC into proper context. Effective doses from CTC (approximately 5 mSv) are similar to the background levels of radiation in the U.S. from naturally occurring sources (national average = 3 mSv/year; range = 1 – 10 mSv/yr). While high doses of radiation have been associated with increased cancer risks, at the low doses used in medical imaging, the effect of radiation is either too small to be convincingly

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[20] Patel MD, Ascher SM, Paspulati RM, et al. Managing Incidental Findings on Abdominal and Pelvic CT and MRI, Part 1: White Paper of the ACR Incidental Findings Committee II on Adnexal Findings. J Am Coll Radiol 2013;10:675-681.
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[27] Hassan C, Pickhardt PJ, Laghi A, et al. Computed tomographic colonography to screen for colorectal cancer, extracolonic cancer, and aortic aneurysm: model simulation with cost-effectiveness analysis. Arch Intern Med. 2008;168:696-705.

demonstrated, or does not exist. Low doses of radiation are defined as those below 100 mSv. Thus, CTC is an extremely low dose procedure, even when tabulating estimated total exposure in a program of CT Colonography-based screening. The National Academies of Sciences (2006), the Health Physics Society (2004), and the American Association of Physicists in Medicine (2011) all discourage the calculation of risk below 50 to 100 mSv, because it is too small to estimate with any accuracy given the available data.

Providers of medical imaging services are engaged in a national effort to keep radiation doses as low as possible while maintaining diagnostic accuracy ("Image Gently®" and "Image Wisely®" web sites). A number of new technologies and approaches are in clinical use to accomplish this task, including the use of exposures that are tailored to the patient size and diagnostic tasks, iterative reconstruction methods, and emerging technologies[28].

The ACRIN trial also used low dose techniques and appropriately modulated dose for smaller and larger patients (to keep image quality constant). Multiple studies have since been performed with

[28] McCollough CH, Chen GH, Kalender W,et al. Achieving routine submillisievert CT scanning: report from the summit on management of radiation dose in CT. Radiology 2012, 264(2), 567-80.

even lower average effective doses with many studies achieving doses in the sub-millisievert range with the aid of iterative reconstruction techniques[29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44].

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[29] Chang KJ, Yee J. Dose reduction methods for CT colonography. Abdom Imaging. 2013; 38(2):224-32.
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[38] Neri E, Faggioni L, Cerri F, et al. CT colonography versus double-contrast barium enema for screening of colorectal cancer: comparison of radiation burden. Abdom Imaging. 2010;35:596-601.
[39] Seuss H, Janka R, Hammon M, et al. Virtual Computed Tomography Colonography: Evaluation of 2D and Virtual 3D Image Quality of Sub-mSv Examinations Enabled by Third-generation Dual Source Scanner Featuring Tin Filtering. Acad Radiol 2018;25:1046-1051.
[40] Shen H, Liang D, Luo M, et al. Pilot study on image quality and radiation dose of CT colonography with adaptive iterative dose reduction three-dimensional. PloS one. 2015;10(1):e0117116.
[41] Shin CI, Kim SH, Lee ES, et al. Ultra-low peak voltage CT colonography: effect of iterative reconstruction algorithms on performance of radiologists who use anthropomorphic colonic phantoms. Radiology. 2014;273:759-771.
[42] Taguchi N, Oda S, Imuta M, et al. Model-based Iterative Reconstruction in Low-radiation-dose Computed Tomography Colonography: Preoperative Assessment in Patients with Colorectal Cancer. Acad Radiol. 2018;25: 415-422.
[43] Yamamura S, Oda S, Imuta M, et al. Reducing the radiation dose for CT colonography: Effect of low tube voltage and iterative reconstruction. Acad Rad 2016;23:155-162.
[44] Yoon MA, Kim SH, Lee JM, et al. Adaptive statistical iterative reconstruction and Veo: assessment of image quality and diagnostic performance in CT colonography at various radiation doses. J Comput Assist Tomogr. 2012;36:596-601.

The controversy of low radiation dose exposure has been reviewed in the literature by experts[45]. Brenner et al. addressed the issue of radiation dose screening with CT colonography and concluded that the benefit-risk ratio was high and that cancer risks were very rare. Brenner concluded that potential lifetime cancer risk for one CTC exam at 50 was 0.14% (0.07% if 70), which could be reduced by factors of five or ten with optimized low dose protocols.

Berrington de Gonzalez et al. examined the benefit to risk ratio in CTC, assuming the radiation dose levels used in the ACRIN National CT Colonography study with CTC screening every five years from ages 50 to 80, along with three micro simulation models for colorectal cancer development, and compared potential lives saved using screening CTC to potential deaths from fatal cancers due to medical radiation[46]. They also included any additional radiation risk from the imaging workup of incidental extracolonic findings. They estimated a large benefit to risk ratio for screening CTC, which varied from 24:1 to 35:1. Thus, even if the highly controversial risk models (such as the linear non-threshold model) used in these studies were accurate, both authors conclude that the benefits of CTC for colorectal screening vastly outweigh the theoretical radiation risks.

Summary

To reiterate, the ACR believes that the above and attached published literature provides continued evidence confirming the efficacy and safety of CTC. We appreciate the opportunity to provide these comments. Should you have any questions or comments, we would welcome further dialogue. Please do not hesitate to contact Kathryn Keysor at (800) 227-5463 extension 4950 or at kkeysor@acr.org.

Sincerely,

Judy Yee, M.D., FACR
Chair, ACR Colon Cancer Committee

References for Comments Made on Online Form

Proposed Analytic Framework:

1. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;**68**:250-281.
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11. Togashi K, Shimura K, Konishi F, et al. Prospective observation of small adenomas in patients after colorectal cancer surgery through magnification chromocolonoscopy. Diseases of the Colon & Rectum 2008;51:196-201.

<u>Key Question #1</u>

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4. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:19777-81.

<u>Key Question #2</u>

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Proposed Research Approach

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Other Relevant CT Colonography Studies

Extracolonic Findings

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Radiation Dose

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