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Diagnostic Accuracy of Laxative-Free Computed Tomographic Colonography for Detection of Adenomatous Polyps in Asymptomatic Adults

A Prospective Evaluation

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Background: Colon screening by optical colonoscopy (OC) or computed tomographic colonography (CTC) requires a laxative bowel preparation, which inhibits screening participation.

Objective: To assess the performance of detecting adenomas 6 mm or larger and patient experience of laxative-free, computer-aided CTC.

Design: Prospective test comparison of laxative-free CTC and OC. The CTC included electronic cleansing and computer-aided detection. Optical colonoscopy examinations were initially blinded to CTC results, which were subsequently revealed during colonoscope withdrawal; this method permitted reexamination to resolve discrepant findings. Unblinded OC served as a reference standard. (ClinicalTrials.gov registration number: NCT01200303)

Setting: Multicenter ambulatory imaging and endoscopy centers.

Participants: 605 adults aged 50 to 85 years at average to moderate risk for colon cancer.

Measurements: Per-patient sensitivity and specificity of CTC and first-pass OC for detecting adenomas at thresholds of 10 mm or greater, 8 mm or greater, and 6 mm or greater; per-lesion sensitivity and survey data describing patient experience with preparations and examinations.

Results: For adenomas 10 mm or larger, per-patient sensitivity of CTC was 0.91 (95% CI, 0.71 to 0.99) and specificity was 0.85 (CI, 0.82 to 0.88); sensitivity of OC was 0.95 (CI, 0.77 to 1.00) and specificity was 0.89 (CI, 0.86 to 0.91). Sensitivity of CTC was 0.70 (CI, 0.53 to 0.83) for adenomas 8 mm or larger and 0.59 (CI, 0.47 to 0.70) for those 6 mm or larger; sensitivity of OC for adenomas 8 mm or larger was 0.88 (CI, 0.73 to 0.96) and 0.76 (CI, 0.64 to 0.85) for those 6 mm or larger. The specificity of OC at the threshold of 8 mm or larger was 0.91 and at 6 mm or larger was 0.94. Specificity for OC was greater than that for CTC, which was 0.86 at the threshold of 8 mm or larger and 0.88 at 6 mm or larger ($P = 0.02$). Reported participant experience for comfort and difficulty of examination preparation was better with CTC than OC.

Limitations: There were 3 CTC readers. The survey instrument was not independently validated.

Conclusion: Computed tomographic colonography was accurate in detecting adenomas 10 mm or larger but less so for smaller lesions. Patient experience was better with laxative-free CTC. These results suggest a possible role for laxative-free CTC as an alternate screening method.

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Colon cancer remains the second most common cause of death from cancer in developed countries, with approximately 50 000 annual deaths expected in the United States (1). Several methods can effectively screen the colon to identify precursor adenomatous polyps, the removal of which decreases disease-specific mortality (2–4). However, structural screening methods require preexamination laxative bowel cleansing. Persons considering screening generally report a strong aversion to laxative preparations, which represents a potentially correctable barrier to participation and contributes to relatively low adherence to colon cancer screening (5, 6).

Accepted practice in colon screening is that adenomas 6 mm or larger should be removed. However, it is also recognized that approximately 90% of lesions with clinically important histology—villous features, high-grade dysplasia, or carcinoma—are 10 mm or larger (2, 7). Recent evaluations of computed tomographic colonography (CTC), a structural, image-based screening examination, show that its ability to detect colonic adenomas 6 mm or larger is similar to that of the current clinical reference, optical colonoscopy (OC) (8–10). Computed tomographic colonography, which to date has required a laxative bowel preparation, has received endorsement by the American Cancer Society as an acceptable method for colon screening (2).

Laxative-free CTC combines the use of low-fiber diet, orally ingested contrast material, and specialized postpro-

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cessing software called *electronic cleansing*. Patients ingest small aliquots of contrast material for 2 days before examination to thoroughly tag feces (11, 12). After image acquisition, the electronic cleansing software digitally subtracts the tagged feces from the colon images, without substantially altering the size or appearance of mucosal folds and polyps (13). Images of the colon are cleansed after image acquisition, without the need for physical preexamination purging.

Computer-aided detection software for CTC is now a standard feature that can be adapted to laxative-free techniques (14–17). The detection software analyzes a colon model computed from the CT images to identify and indicate polyp candidates and can improve the performance of human readers (15–18).

This article describes the results of a clinical screening study using laxative-free CTC augmented by computer-aided detection. As an initial step to potentially address the adverse effect of laxative preparations on screening, our purpose was to assess the diagnostic performance of laxative-free CTC for detection of colonic adenomas 6 mm or larger and to preliminarily compare it with OC. We also tested the hypothesis that patient experience would improve with laxative-free preparation versus standard cathartic preparation.

Context

Although computed tomographic colonography (CTC) has been shown to be an acceptable method to screen for colorectal cancer in patients who decline optical colonoscopy, both types of screening require a laxative preparation, which remains a barrier to screening.

Contribution

Participants in this study had laxative-free CTC after ingestion of oral contrast and the use of a computer program to electronically "cleanse" the colon for radiologic evaluation. Compared with optical colonoscopy performed in the same patients, laxative-free CTC performed well at detecting adenomas 10 mm or larger.

Caution

The study involved a limited number of expert radiologist readers.

Implication

Laxative-free CTC may provide an alternative for persons in whom laxative bowel preparation is a barrier to colorectal cancer screening.

—The Editors

METHODS

Setting and Participants

We recruited participants from 4 institutions (Massachusetts General Hospital; Brigham and Women's Hospital; University of California, San Francisco Veterans Affairs Medical Center; and North Shore Medical Center) after obtaining institutional review board approval and informed written consent. All study data were handled in accordance with the Health Insurance Portability and Accountability Act.

Between June 2005 and October 2010, we recruited asymptomatic men and women aged 50 to 85 years. We excluded persons who had melena or hematochezia in the past 6 months; positive results on fecal occult blood testing in the past year; previous colonoscopy, sigmoidoscopy, CTC, or barium enema in the past 5 years; or a history of polyposis, colorectal cancer, or inflammatory bowel disease. Persons with a personal history of polyps (but not the polyposis syndrome or cancer) were eligible, provided that they had not received colon screening in the 5 years before recruitment.

Recruitment began with the OC schedules at each participating site. With institutional review board approval, study staff screened the schedules, identifying potential participants who met inclusion and exclusion criteria. We then sought permission from each candidate's primary care physician or gastroenterologist before initiating recruitment contact. All consecutive, eligible patients from whom we obtained physician consent were contacted for potential recruitment.

Computed Tomographic Colonography

Appendix Table 1 (available at www.annals.org) provides details on the laxative-free preparation for CTC. We used iohexol 300 (GE Healthcare, Chalfont St. Giles, United Kingdom), a low-osmolar, nonionic iodinated agent for tagging. Computed tomographic colonography examinations at all sites were performed on 16- or 64-channel multidetector CT scanners by using single-breath-hold prone and supine positioning; low-radiation-dose protocol (120 kVp, 50 mAs effective), including electronic carbon dioxide insufflation with the PROTOCO$_2$L Colon Insufflator (Bracco, Milan, Italy); and no spasmolytic. Detectors were configured for maximum 2.5-mm *z*-axis length with 1.25-mm overlap interval. Radiology staff performed quality control for all insufflations by using scout and selected axial images.

CTC Interpretation and Radiologist Training

Study CTCs were performed on participants consecutively, guided by the OC schedule. A team of 3 abdominal radiologists, all of whom worked at Massachusetts General Hospital, interpreted the CTC examinations. Each radiologist worked independently and interpreted CTC results in a series of regularly scheduled 4-hour reading sessions, with 1 radiologist assigned, in rotating sequence, per session.

Readers selected cases consecutively from an updated queue, always starting with the most recent available. They were allowed only 1 interpretation of each case. We estimated aggregate performance of CTC by uniformly using the first interpretation logged for each case. The first inter-

pretation was also uniformly used for segmental unblinding (see Reference Standards section).

To facilitate interreader comparisons of performance, we encouraged readers to read as many cases as feasible from the queue. We expected that each reader, who remained blinded to other CTC interpretations, OC results, and pathology reports, would read most cases. Variability in reader case volume was expected because of scheduling and interpretation speed of the reader but not any characteristic of the cases. Each reader interpreted examination results acquired from all participating institutions.

Before study inception, each radiologist had interpreted more than 200 clinical CTC results and 20 laxative-free training examinations, the latter of which were performed with the study protocol. Readers were trained to use electronic cleansing and computer-aided detection systems. We did not formally test readers before participation in the study. However, as a benchmark for subsequent comparison, the positive predictive value for each radiologist based on clinical CTC interpretations between 2003 and 2005 for histopathologically confirmed adenomas 6 mm or larger was 50% (20 out of 40), 54% (14 out of 26), and 71% (10 out of 14). The range of these values was similar to previous investigations of CTC, and we expected them to exceed those of the study because of lower prevalence of lesions in a screening cohort (8, 19).

All interpretations were performed on a single V3D workstation, version 2.1.3 (Viatronix, Stony Brook, New York), modified to include proprietary electronic cleansing and computer-aided detection software. The cleansing and detection software were fixed throughout the study, both subsystems were used by default for all interpretations, and readers could toggle each on or off. Detailed descriptions of the cleansing and detection software have been given in previous technical publications. The electronic cleansing included Hessian analysis, level set evolution, and mucosal reconstruction (20).

The computer-aided detection software identified polyp candidates first by calculating a curvature index of the mucosal surface of the colonic mucosa as extracted from the interpolated source CT images; features demonstrating internal convexity along 2 axes were included as potential polyp candidates. Local texture features, such as attenuation variance and mean attenuation, were then combined with curvature values into feature vectors that were filtered for false-positive reduction by a Bayesian neural network trained on a separate cohort (21, 22). Detection marks were visible as readers made their manual interpretations to balance time-saving and improvement of interpretation. To avoid indication fatigue, the detection system presented a maximum of the 6 most probable polyp candidates per CT image series.

Both primary 2- and 3-dimensional interpretation modes were available; each radiologist chose and recorded his or her approach. Primary 2-dimensional interpretation refers to the evaluation of axial and multiplanar reconstructions to detect polyps, and primary 3-dimensional technique refers to the evaluation of an endoluminal model to detect lesions (23). Problem solving for each interpretation technique incorporates the use of the opposing reading method.

We recorded interpretation times and reader confidence about the presence of polyps by using a scale from 0 (a polyp definitely was not present) to 9 (a polyp definitely was present). Radiologists assessed colonic and incidental extracolonic findings by using the CTC reporting and data system (C-RADS)—a standardized schema codifying technical adequacy of imaging, as well as the clinical severity of colonic and extracolonic abnormalities. We reported these scores on the basis of the first interpretation for each study examination (24). To further explore the effect of cleansing software on imaging, radiologists also reported subjective assessments of image quality on a scale of 1 (no perceivable artifacts) to 5 (uninterpretable due to artifacts). Readers were instructed to measure all polyps 6 mm or larger. We tabulated the effective x-radiation for each CT examination.

Optical Colonoscopy

Optical colonoscopy for each participant was scheduled within 5 weeks of CTC by using a protocol standardized across all sites. Preparation for OC consisted of fiber restriction for 1 to 2 days and 2 to 4 L of polyethylene glycol cathartic ingested the night before the examination. Fellowship-trained staff gastroenterologists performed colonoscopies by using monitored conscious-sedation protocol and video-assisted instruments.

Reference Standards

Lesion presence and location were confirmed by segmental unblinding of OC (9). For each case, the previously recorded CTC interpretation was revealed to the gastroenterologist after withdrawal of the colonoscope segment by segment from the proximal colon (first-pass OC). When CTC and first-pass OC readings were discrepant, the gastroenterologist could reinsert the colonoscope to confirm the presence or absence of lesions in a particular segment of colon. The second CTC-informed colonoscopic pass was used as a reference standard for lesion presence, permitting comparison of CTC and first-pass OC.

Description of resected specimens in the official clinical pathology report served as a reference for lesion histology. Advanced adenomas were defined as lesions showing high-grade dysplasia, more than 25% villous components on the pathology specimen, or a size of 10 mm or larger. We grouped serrated sessile adenomas and other adenomas together unless they had specific features of advanced adenoma.

The primary study metric was performance for adenoma detection. In this context, hyperplastic lesions were considered false-positive detections. However, we also performed a separate analysis for detection of all lesions, without histology restriction.

Lesion size was established by 1 of 2 co-investigators who were experienced with CTC and not otherwise involved in case interpretation. These retrospective measurements of confirmed target lesions were made by using the CTC images and were informed of both OC and pathology results.

Standard practice for OC at each study institution was to assess lesion size without formal measurement rulers. Previous investigations of CTC, OC, and pathology measurements have demonstrated that size estimates by using CTC are both more precise and more accurate than those of OC (25). As in vivo estimates, CTC measurements avoid postexcision changes associated with pathology specimens. If the retrospective review failed to identify a confirmed lesion on CTC, the pathology report was used to estimate lesion size. When retrospective review failed and polyps had been fulgurated, not retrieved, or retrieved piecemeal, the size according to the OC was used.

Co-investigators not involved in examination interpretations compared the prospective study readings with the reference standard during the retrospective reviews. They used the established algorithm permitting location matches between CTC and OC within 1 colonic segment and size matches within 50% of the reference standard (8, 9, 26).

Survey Data

Participants recorded experiences preparing for and undergoing laxative-free CTC and OC on a written questionnaire, which was self-administered and completed without assistance from study staff as each preparation and examination step was completed. For each preparation, participants recorded discomfort, difficulty of completion, and severity of bowel symptoms on a 5-point scale (for discomfort, 1 indicated no discomfort and 5 indicated severe pain; for completion, 1 indicated no difficulty completing and 5 indicated extremely difficult completing; for bowel symptoms, 1 indicated no bowel habit changes and 5 indicated severe bowel habit changes—1 indicated the best response throughout). Finally, participants reported binary preference for CTC versus OC ("If you had to choose which test to have again, which would you prefer?"). The questionnaire was not separately validated before use in the study.

Extracolonic Findings

We tabulated the frequency of diagnostic evaluations initiated by incidental extracolonic findings detected in the CTC examinations. The **Appendix** (available at www.annals.org) explains details of this accounting process.

Statistical Analysis

Study recruitment was guided by an expected 12% prevalence of adenomas 6 mm or larger in a screening cohort and a point estimate of 80% sensitivity for these target lesions (27, 28). We planned to recruit approximately 600 participants to achieve margins of sampling error of approximately 8 percentage points for sensitivity. This sample would also allow 90% power to detect differences in sensitivity between CTC and OC of 18 percentage points or more (9).

For lesions 8 mm or larger, this sample size allowed for margins of error of approximately 14 percentage points for sensitivity, assuming a prevalence of 6% and a sensitivity of 85%. For lesions 10 mm or larger, this sample size allowed for margins of error of approximately 12 percentage points, assuming a prevalence of 4% and a sensitivity of 90%. We did not expect power greater than 80% to detect differences in sensitivities as small as 18 percentage points for these larger lesions (8). Performance and interpretation of study examinations continued through December 2010, reflecting achievement of recruitment goals.

For per-patient calculations, we set a target size threshold at which CTC examination results were deemed positive and subsequently determined whether the reference standard confirmed the presence of an adenoma of appropriate size (8). For reporting purposes, lesions were categorized by 3 size thresholds: 6, 8, and 10 mm or larger. The thresholds reflect increasing clinical significance based on lesion size and permit detailed assessment of test performance.

We defined a positive test result for CTC as identification of a polyp 6 mm or larger. This determination was then deemed either true-positive or false-positive for a given reporting size threshold (that is, 6, 8, or 10 mm or larger), depending on whether the reference standard confirmed that a lesion of the appropriate reporting size threshold was present. Negative results of CTC testing were similarly deemed either true-negative or false-negative at each reporting threshold, depending on the result of the reference standard.

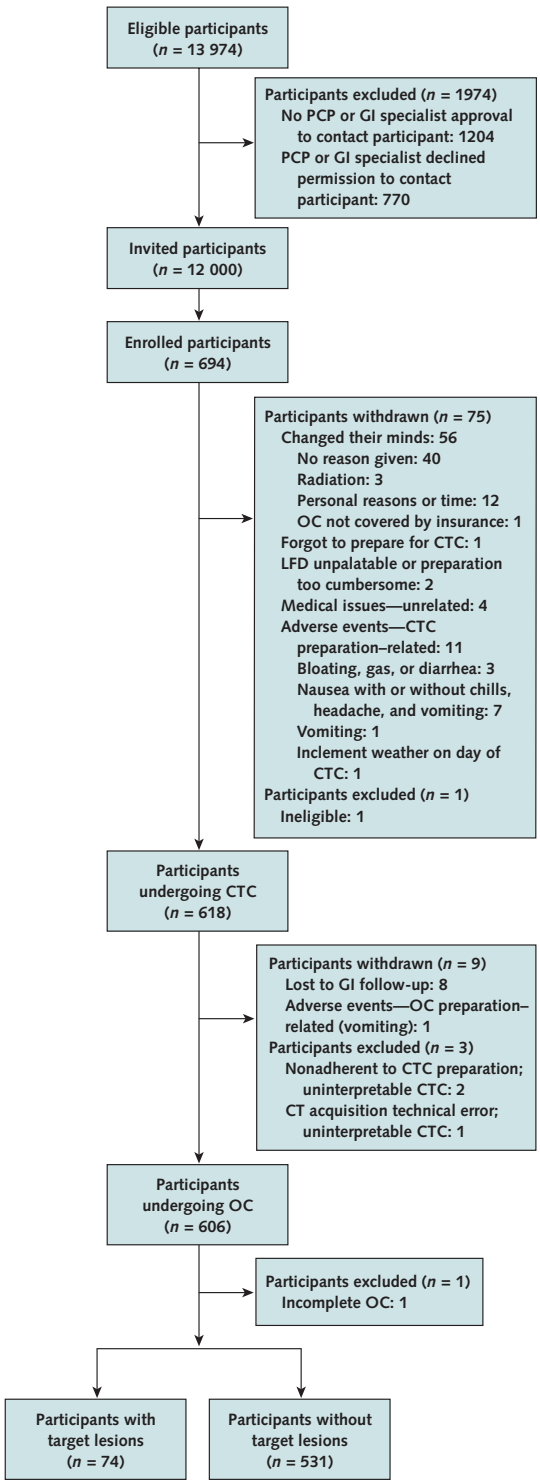
For per-polyp analysis, prospective determinations by radiologists at the time of CTC reading had to match the reference standard for segmental location as well as size. The same procedure was used to evaluate first-pass OC. Participants without complete CTC and OC results were excluded.

We calculated sensitivity of CTC and first-pass OC on a per-patient and per-polyp basis and specificity, positive and negative predictive values, and receiver-operating characteristic (ROC) curves on a per-patient basis. For ROC curve generation, reader confidence scores of 0 to 4 were interpreted as "case-negative" and scores of 5 to 9 as "case-positive." We compared the sensitivity and specificity of CTC and first-pass OC by using McNemar tests.

To explore variability across readers, we calculated the area under the ROC curve from matched cases read by all 3 readers. In addition, for each set of readers, we calculated pair-wise κ statistics for sensitivity to detect lesions 10 mm or larger. We tabulated the distribution of C-RADS scores for each interpretation (24).

We calculated 95% CIs for sensitivity, specificity, and positive and negative predictive values by using exact binomial methods. We calculated ROC curves by using LABMRMC (Kurt Rossman Laboratories, University of

Figure 1. **Study flow diagram.**



A total of 605 participants completed the study protocol and yielded complete data sets for interpretation and comparison: 76 were recruited from Brigham and Women's Hospital, 479 from Massachusetts General Hospital, 1 from North Shore Medical Center, and 49 from the University of California, San Francisco, Veterans Affairs Medical Center. CTC = computed tomographic colonography; GI = gastrointestinal; LFD = low-fiber diet; OC = optical colonoscopy; PCP = primary care provider.

Chicago, Chicago, Illinois). We compared survey scores by using Kruskal–Wallis tests and binary preferences by using chi-square tests. Criterion for statistical significance throughout was a 2-tailed P value less than 0.05. We used InStat 3.0 (GraphPad Software, La Jolla, California) and SAS 9.1 (SAS Institute, Cary, North Carolina) for analyses.

Role of the Funding Source

The study was primarily funded by investigator-initiated grants from GE Healthcare and the American Cancer Society, with additional funding from the National Institutes of Health. The funding sources had no role in the design, execution, analysis, report drafting, or submission of this study.

RESULTS

We enrolled 694 qualifying study participants and obtained complete CTC, OC, and pathology data from 605 (**Figure 1**). **Table 1** shows the characteristics of the study cohort. There were no significant differences in demographic characteristics of the study cohort compared with those eligible but not enrolled ($P > 0.20$ for all comparisons). **Table 2** shows characteristics of confirmed target lesions, and **Figure 2** shows representative CTC and OC images.

Of confirmed lesions with advanced histology, 85% (22 of 26) were 10 mm or larger. Of the 4 advanced lesions smaller than 10 mm, 1 demonstrated high-grade dysplasia and 3 demonstrated villous features. Three incidences of cancer were confirmed, all of which were larger than 10 mm. The mean interval between CTC and OC was 17 days (SD, 30).

Reading Time, Image Quality, and Reader Variability

The 3 readers independently interpreted 573, 482, and 567 cases, respectively. The mean time for CTC interpretation was 14.1 minutes (SD, 5). Readers 1 and 2 used a 2-dimensional method for detection, and reader 3 used a 3-dimensional technique. Median scores of image quality reported by the readers ranged from 2 to 3. The κ statistic for comparison of reader sensitivity for polyp detection between 2-dimensional readers was 0.60 (95% CI, 0.41 to 0.78) and that for comparison of 2-dimensional versus 3-dimensional readers ranged from 0.31 (CI, 0.10 to 0.47) to 0.39 (CI, 0.24 to 0.54). Individual reader performance seemed to be generally better for the 2-dimensional technique (**Appendix Table 2**, available at www.annals.org).

Performance Characteristics per Patient

Table 3 shows per-patient performance of CTC and first-pass OC. For adenomas 10 mm or larger, per-patient sensitivity of laxative-free CTC was 0.91 (CI, 0.71 to 0.99) and specificity was 0.85 (CI, 0.82 to 0.88); per-patient sensitivity for OC was 0.95 (CI, 0.77 to 1.00) and specificity was 0.89 (CI, 0.86 to 0.91). Negative predictive values of CTC and OC were both 1.00 (CI, 0.99 to 1.00).

Table 1. **Characteristics of Study Cohort**

Characteristic	No Cancer or Adenoma ≥6 mm (*n* = 531)	Cancer or Adenoma ≥6 mm and <10 mm (*n* = 52)	Cancer or Adenoma ≥10 mm (*n* = 22)	Total (*n* = 605)
Age, *y*				
Mean	59.9	64.6	63.1	60.4
Interquartile range	50–80	50–78	50–74	50–80
Sex, *n (%)*				
Men	273 (51)	35 (67)	14 (64)	322 (53)
Women	258 (49)	17 (33)	8 (36)	283 (47)
Race or ethnic group, *n (%)*				
American Indian or Alaskan native	0	0	0	0
Asian	10 (2)	1 (2)	1 (5)	12 (2)
Black	22 (4)	0	0	22 (4)
Native Hawaiian or other Pacific Islander	1 (<1)	0	0	1 (<1)
White	475 (89)	49 (94)	21 (95)	545 (90)
Unknown or missing	23 (4)	2 (4)	0	25 (4)
Hispanic ethnicity, *n (%)*				
No	508 (96)	50 (94)	22 (100)	580 (96)
Yes	10 (2)	1 (2)	0	11 (2)
Unknown	13 (2)	1 (2)	0	14 (2)
Medical history of polyps or colon cancer, *n (%)*				
Family history of colon cancer or polyps	98 (18)	6 (12)	3 (14)	107 (18)
Personal history of polyps	99 (19)	22 (42)	2 (9)	123 (20)
Both family history of colon cancer or polyps and personal history of polyps	2 (<1)	0	0	2 (<1)

For adenomas, first-pass OC sensitivity was higher than that for CTC. *P* values for these performance differences were 1.00 at thresholds of 10 mm or larger, 0.124 at thresholds of 8 mm or larger, and 0.06 at 6 mm or larger. The specificity of OC was greater than that of CTC at the 8 mm or larger ($P = 0.02$) and 6 mm or larger ($P = 0.001$) thresholds but not at the 10 mm or larger threshold ($P = 0.08$).

No serendipitous detection of polyps on second-pass OC occurred in the absence of a corresponding detection on CTC. Per-patient sensitivity to detect polyps 6 mm or larger of any histology by CTC was 0.47 (CI, 0.38 to 0.56); this result was lower than that of OC, which was 0.59 (CI, 0.50 to 0.68) ($P = 0.06$). Mean effective radiation dose per CTC was 5.3 mSv (SD, 2.1).

Performance Characteristics per Lesion

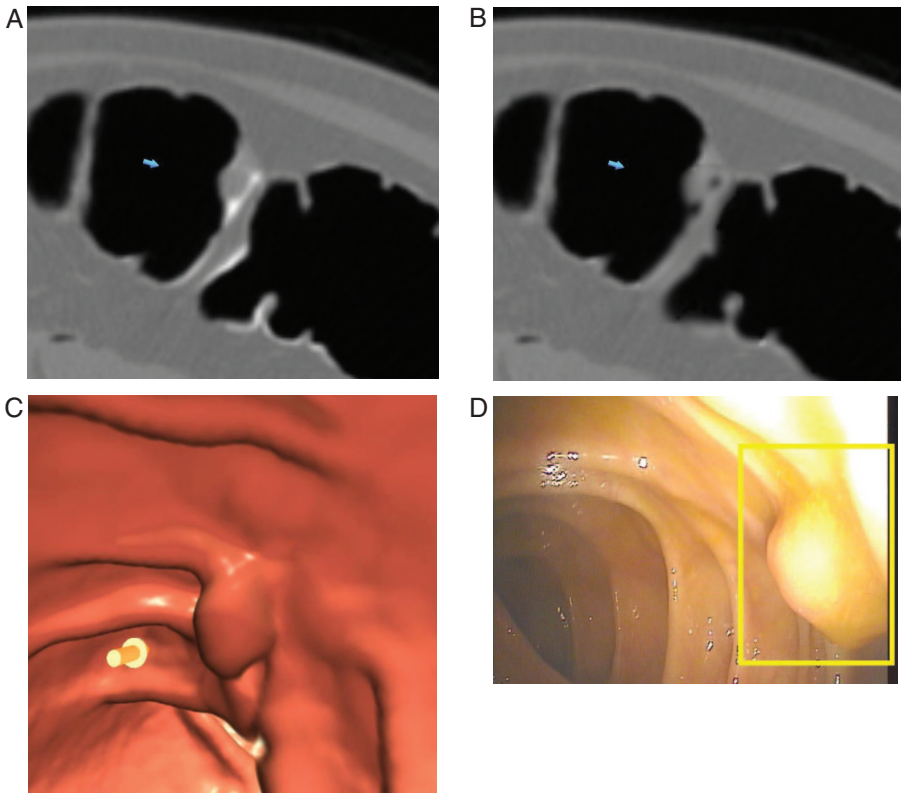
Table 3 summarizes the performance of per-lesion detection. Both CTC and OC detected all 3 cases of colon

Table 2. **Characteristics of Polyps Confirmed by OC and Histopathology**

Segment	Histologic Type	Lesions Detected, *n*		
		6–9 mm	≥10 mm	Total
Rectum	Adenoma or carcinoma	3	4	7
	Nonadenomatous lesion	19	2	21
Sigmoid	Adenoma or carcinoma	14	8	22
	Nonadenomatous lesion	25	1	26
Descending colon	Adenoma or carcinoma	9	0	9
	Nonadenomatous lesion	9	3	12
Transverse colon	Adenoma or carcinoma	14	6	20
	Nonadenomatous lesion	6	1	7
Ascending colon	Adenoma or carcinoma	28	2	30
	Nonadenomatous lesion	9	5	14
Cecum	Adenoma or carcinoma	5	2	7
	Nonadenomatous lesion	6	3	9
Total	Adenoma or carcinoma	73	22	95
	Advanced adenoma or carcinoma	4	22	26
	Nonadenomatous lesion	74	15	89

OC = optical colonoscopy.

Figure 2. **Colonic adenoma as seen on laxative-free CTC and OC.**



CTC = computed tomographic colonography; OC = optical colonoscopy. **A.** Zoomed axial 2-dimensional CTC image before electronic cleansing. **B.** Zoomed axial 2-dimensional CTC image after electronic cleansing. **C.** Endoluminal 2-dimensional CTC image. Yellow arrow represents computer-aided detection marker placed automatically by the computer to assist the reader; computer-aided detection markers were available for both 2- and 3-dimensional views. The blue arrows in panels A and B indicate the point of view for 3-dimensional reconstruction (*C*). **D.** OC image of confirmed 12-mm adenoma prospectively identified by CTC colonography and OC in an asymptomatic 63-year-old male study participant. The yellow box is an annotation placed manually by the gastroenterologist to highlight the polyp for the colonoscopy report.

cancer. At the 10 mm or larger threshold, the sensitivity of CTC was 0.82 (CI, 0.66 to 0.95) and that of OC was 0.95 (CI, 0.77 to 1.00); differences in performance at thresholds of 10 mm or larger ($P = 0.35$) or 8 mm or larger ($P = 0.15$) were not significant. At a threshold of 6 mm or larger, the sensitivity of CTC was less than that of OC ($P = 0.005$).

The mean size of adenomas missed by CTC was 7 mm (SD, 2). A total of 15 lesions were identified by CTC, missed by first-pass OC, and detected on second-pass (unblinded) OC. Five of these lesions were adenomas, all of which were smaller than 6 mm.

First-pass OC missed 7 lesions that were also 6 mm or larger; all of these were hyperplastic. In addition, first-pass OC misclassified 24 adenomas 6 mm or larger because of underestimation of their size. Sensitivity for detection of advanced adenomas of 6 mm or larger by CTC was 0.69 (CI, 0.60 to 0.78) and that by OC was 0.88 (CI, 0.81 to 0.95) ($P = 0.08$). Sensitivity to detect polyps 6 mm or larger of any histology by CTC was 0.48 (CI, 0.40 to 0.55) and was lower than that of OC, which was 0.65 (CI, 0.58 to 0.72) ($P = 0.002$).

For adenomas, 74% (31 out of 42) of false-negative results on CTC involved examinations with image quality scores of 3 or lower (1 indicates the most favorable response). False-negative results for adenomas by CTC and OC were approximately evenly distributed with respect to segment. For CTC, 33% (14 out of 42) of false-negative results occurred in the rectum, sigmoid, or descending colon; 17% (7 out of 42) in the transverse colon; and 50% (21 out of 42) in the ascending colon and cecum. For OC, corresponding distribution for false-negative results was 35% (8 out of 23) in the rectum, sigmoid, or descending colon; 26% (6 out of 23) in the transverse colon; and 39% (9 out of 23) in the ascending colon or cecum.

CTC Reporting and Data System Scores and Extracolonic Findings

Readers rated 97.1% (588 out of 605) of cases technically adequate and 6.1% (37 out of 605) as C-RADS scores of C3 or C4, indicating polyps or masses 10 mm or larger. A total of 140 extracolonic indeterminate or potentially clinically important (C-RADS scores of E3 or E4) incidental findings were observed in 113 study cases; 16%

Table 3. **Performance for Detection of Polyps by Laxative-Free CTC and OC***

Characteristic	Reference Size of Confirmed Adenoma or Carcinoma					
	≥6 mm		≥8 mm		≥10 mm	
	CTC	OC	CTC	OC	CTC	OC
Performance by participant						
True-positive results, *n*	44	56	28	35	20	21
False-negative results, *n*	30	18	12	5	2	1
True-negative results, *n*	469	500	487	513	497	517
False-positive results, *n*	62	31	78	52	86	66
Sensitivity						
Value (95% CI)	0.59 (0.47–0.70)	0.76 (0.64–0.85)	0.70 (0.53–0.83)	0.88 (0.73–0.96)	0.91 (0.71–0.99)	0.95 (0.77–1.00)
Participants with lesions, *n*	74	74	40	40	22	22
Specificity						
Value (95% CI)	0.88 (0.85–0.91)	0.94 (0.92–0.96)	0.86 (0.83–0.89)	0.91 (0.88–0.93)	0.85 (0.82–0.88)	0.89 (0.86–0.91)
Participants without lesions, *n*	531	531	565	565	583	583
Positive predictive value						
Value (95% CI)	0.42 (0.32–0.51)	0.64 (0.53–0.74)	0.26 (0.18–0.36)	0.40 (0.30–0.51)	0.19 (0.12–0.28)	0.24 (0.16–0.35)
Positive test results, *n*	106	87	106	87	106	87
Negative predictive value						
Value (95% CI)	0.94 (0.92–0.96)	0.97 (0.95–0.98)	0.98 (0.96–0.99)	0.99 (0.98–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Negative test results, *n*	499	518	499	518	499	518
Positive likelihood ratio						
Value (95% CI)	5.09 (3.77–6.88)	12.96 (9.00–18.68)	5.07 (3.80–6.77)	9.51 (7.16–12.63)	6.16 (4.87–7.80)	8.43 (6.60–10.77)
Negative likelihood ratio						
Value (95% CI)	0.46 (0.35–0.61)	0.26 (0.17–0.39)	0.35 (0.22–0.56)	0.14 (0.06–0.31)	0.11 (0.03–0.40)	0.05 (0.01–0.35)
Area under ROC curve						
Value (95% CI)	0.80 (0.77–0.83)	–	0.84 (0.81–0.87)	–	0.94 (0.92–0.96)	–
Participants, *n*	605	–	605	–	605	–

Characteristic	Reference Size of Confirmed Polyp, Any Histology					
	≥6 mm		≥8 mm		≥10 mm	
	CTC	OC	CTC	OC	CTC	OC
Performance by participant						
True-positive results, *n*	60	76	37	45	23	31
False-negative results, *n*	69	53	26	18	14	6
True-negative results, *n*	430	465	473	500	485	512
False-positive results, *n*	46	11	69	42	83	56
Sensitivity						
Value (95% CI)	0.47 (0.38–0.56)	0.59 (0.50–0.68)	0.59 (0.46–0.71)	0.71 (0.59–0.82)	0.62 (0.45–0.78)	0.84 (0.68–0.94)
Participants with lesions, *n*	129	129	63	63	37	37
Specificity						
Value (95% CI)	0.90 (0.87–0.93)	0.98 (0.96–0.99)	0.87 (0.84–0.90)	0.92 (0.90–0.94)	0.85 (0.82–0.88)	0.90 (0.87–0.92)
Participants without lesions, *n*	476	476	542	542	568	568

Sensitivity, per Polyp	Reference Size of Confirmed Polyp					
	≥6 mm		≥8 mm		≥10 mm	
	CTC	OC	CTC	OC	CTC	OC
Adenoma or carcinoma						
True-positive results, *n*	53	72	32	38	18	21
False-negative results, *n*	42	23	14	8	4	1
Value (95% CI)	0.56 (0.45–0.66)	0.76 (0.66–0.84)	0.70 (0.54–0.82)	0.83 (0.69–0.92)	0.82 (0.60–0.95)	0.95 (0.77–1.00)
Lesions, *n*	95	95	46	46	22	22
Lesions, any histology						
True-positive results, *n*	88	120	39	54	19	31
False-negative results, *n*	96	64	37	22	18	6
Value (95% CI)	0.48 (0.40–0.55)	0.65 (0.58–0.72)	0.51 (0.40–0.63)	0.71 (0.60–0.81)	0.51 (0.34–0.68)	0.84 (0.68–0.94)
Lesions, *n*	184	184	76	76	37	37

CTC = computed tomographic colonography; OC = optical colonoscopy; ROC = receiver-operating characteristic.

* Sensitivity refers to the fraction of participants with confirmed lesions (of the specified size) that were prospectively identified by CTC and first-pass OC. Specificity refers to the fraction of participants without confirmed lesions similarly categorized prospectively by CTC and first-pass OC. Positive predictive value is the fraction of participants with CTC or first-pass OC findings (of the specified size) also confirmed by the reference standard. Negative predictive value is the fraction of participants without lesions of the specified size detected on CTC who also had no lesions confirmed by the reference standard. For analyses of adenoma detection, hyperplastic lesions were treated as false-positive results for both CTC and OC. The ROC curve plots sensitivity versus the false-positive rate and the area under the ROC curve indicates the accuracy of CTC. Scalar confidence data necessary for calculation of ROC curves was available for CTC but not for OC. CTC and OC interpretations were deemed positive for prospective identification of lesions ≥6 mm.

(97 out of 605) of study cases had indeterminate findings (E3) and 3% (16 out of 605) had potentially clinically important findings (E4).

Extracolonic findings associated with C-RADS scores of E3 or E4 were distributed anatomically, with 31% (43 out of 140) occurring in the chest, 22% (31 out of 140) in the gastrointestinal tract, 40% (56 out of 140) in the genitourinary tract, 0.7% (1 out of 140) in the vasculature, and 2.9% (4 out of 140) in the musculoskeletal system. Review of medical records revealed that 5.5% (33 out of 605) of study participants subsequently had additional diagnostic work-up because of extracolonic findings reported on index CTC.

Adverse Events and Incomplete Participation

No adverse events relating to the CTC preparation or examination that required treatment occurred. No reported perforations or major bleeding occurred related to OC. Eleven participants withdrew because of CTC preparation–related adverse events (2 from bloating or gas, 1 from diarrhea, 7 from nausea, and 1 from vomiting). Eight participants withdrew after CTC but before OC preparation and were lost to follow-up. One participant withdrew because of vomiting during OC preparation. In total, 2% (13 out of 618) of participants who had CTC were excluded because of incomplete data.

Participant Experience

A total of 92.4% (559 out of 605) of participants completed the survey and reported median comfort scores of 1 (CTC) and 2 (OC), median scores reflecting difficulty completing each preparation of 2 (CTC) and 3 (OC), and median scores about severity of bowel habit changes of 2 (CTC) and 4 (OC) ($P < 0.001$ for all comparisons). A total of 76.9% (465 out of 605) of participants expressed a binary preference about future examinations; of these, 290 preferred CTC and 175 preferred OC ($P < 0.001$).

DISCUSSION

In this study of diagnostic accuracy, laxative-free, computer-aided CTC correctly identified 91% of persons with adenomas 10 mm or larger. Moreover, patients reported a better experience with CTC examination preparation over standard, cathartic preparation. Readers deemed most cases adequate for interpretation, and we observed no major adverse events with either technique. These results suggest that laxative-free CTC can detect the most clinically important polyps and could contribute to colon cancer screening.

Overall performance for adenoma detection of laxative-free CTC was lower than that of first-pass OC. At the 8 mm or larger and 6 mm or larger thresholds, the magnitude of observed differences in sensitivity on a per-patient basis could be considered clinically significant, even though the size of our study limited our ability to resolve these differences as statistically significant. However, the adenomas smaller than 10 mm that CTC tended to miss were also less likely to have clinically important histologic findings of high-grade dysplasia, villous features, or invasive cancer. In screening cohorts, polyps 10 mm or larger account for approximately 90% of lesions having these concerning histologic features, which our observations confirmed (7, 10, 29–31).

By using the C-RADS structured-reporting scheme, reader interpretations resulted in additional diagnostic work because of incidental extracolonic findings in 5.5% of cases. Radiation dose for CTC was approximately 30% of the median dose of diagnostic abdominal computed tomography, a level deemed acceptable for mass screening (32, 33). The zero-fiber meal kit that we used is no longer marketed but is readily replaceable by other commercial products.

Other investigations of laxative-free CTC in symptomatic, nonscreening cohorts have shown encouraging performance similar to what we observed (27, 28, 34, 35). In this study, we evaluated a larger screening cohort with lower prevalence of polyps and implemented electronic cleansing and computer-aided detection in prospective readings. An English-language MEDLINE search to December 2011 revealed several large, well-designed comparison studies, all involving full laxative preparations and none using computer-aided detection. The performance of laxative-free CTC for detection of lesions 10 mm or larger in our study seems similar to that of the National Colonography Study and 2 other recent prospective studies but somewhat lower than the 2003 Department of Defense trial (8, 26, 36, 37).

Our study was limited by size, number of readers, and quality of the survey data. Restricting study to a low-risk cohort limited the prevalence of lesions and the study's statistical power, especially for polyps 10 mm or larger. However, evaluation in a screening-type cohort is essential, as the performance of human readers can vary with expected prevalence of disease. Only a small fraction of eligible persons participated in this study; although representative of the larger population, this further limited the generalizability of our results.

Having only 3 readers limited our understanding of the observed variations in reader performance. Across all size ranges, detection performance with the 3-dimensional technique seemed lower than that of the 2-dimensional technique. In the National Colonography Study, no such differences in performance were observed (8). Given the similarity in prestudy performance among our readers, the variability that we observed in their performance suggests that interpretation technique may have greater influence in laxative-free CTC.

This finding may be due to 3-dimensional artifacts that arise with electronic cleansing, which can mimic small polyps. Our design did not permit us to separately assess either this effect or the benefit of computer-aided detection, the latter having been uniformly used by all readers. A

multireader, multicase ROC analysis should be possible as a follow-up study to address these topics. Finally, our survey instrument was not separately validated for portrayal of participant experiences, and the sequential nature of the study protocol may have introduced recall bias that could have influenced survey responses; hence, the patient preferences that we observed should be regarded as initial assessments.

Decision modeling suggests that CTC is more cost-effective than no screening and may be cost-effective compared with OC if CTC substantially improves screening participation, which has recently been shown (38, 39). Laxative-free CTC addresses an important barrier to screening, and its potential effect on screening merits further investigation.

In summary, we observed that laxative-free CTC could accurately identify asymptomatic persons with adenomas 10 mm or larger but performed less well for smaller lesions. Our results suggest a role for CTC as an alternate screening method to OC with which participants would experience improved preparation and examination comfort—factors that could contribute positively to overall screening participation.

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Appendix

For all study participants, we retrospectively reviewed findings and recommendations for follow-up described in index CTC examinations. We then examined the medical records of participants for all radiologic and nonradiologic follow-up diagnostic and therapeutic procedures initiated by the observations of the index CTC. Thus, we tabulated the frequency with which findings reported in the index (study) CTC examinations led to additional diagnostic work-up of incidental extracolonic findings.

Appendix Table 1. **Laxative-Free CTC Preparation**

Preparation Component	2 Days Before CTC	1 Day Before CTC	Day of CTC
Tagging (iohexol 300 [GE Healthcare, Chalfont St. Giles, United Kingdom])	5 mL in 300-mL beverage, with meals and snacks	5 mL in 300-mL beverage, with meals and snacks	15 mL in 900-mL beverage
Hydration	300 mL twice daily	300 mL twice daily	–
Diet modification	Low fiber	Zero-fiber meal kit (Nutraprep [Bracco, Milan, Italy])	–

CTC = computed tomographic colonography.

Appendix Table 2. Performance of Individual Readers of CTC for Detection of Adenomas*

Characteristic	Reference Size of Confirmed Adenoma or Carcinoma								
	≥6 mm			≥8 mm			≥10 mm		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Performance by participant									
True-positive results, *n*	50	24	29	31	20	23	19	15	15
False-negative results, *n*	22	34	41	7	12	16	1	2	6
True-negative results, *n*	406	411	457	421	433	482	427	443	492
False-positive results, *n*	95	13	40	114	17	46	126	22	54
Sensitivity									
Value (95% CI)	0.69 (0.57–0.80)	0.41 (0.29–0.55)	0.41 (0.30–0.54)	0.82 (0.66–0.92)	0.63 (0.44–0.79)	0.59 (0.42–0.74)	0.95 (0.75–1.00)	0.88 (0.64–0.99)	0.71 (0.48–0.89)
Participants with lesions, *n*	72	58	70	38	32	39	20	17	21
Specificity									
Value (95% CI)	0.81 (0.77–0.84)	0.97 (0.95–0.98)	0.92 (0.89–0.94)	0.79 (0.75–0.82)	0.96 (0.94–0.98)	0.91 (0.89–0.94)	0.77 (0.73–0.81)	0.95 (0.93–0.97)	0.90 (0.87–0.92)
Participants without lesions, *n*	501	424	497	535	450	528	553	465	546
Positive predictive value									
Value (95% CI)	0.34 (0.27–0.43)	0.65 (0.47–0.80)	0.42 (0.30–0.55)	0.21 (0.15–0.29)	0.54 (0.37–0.71)	0.33 (0.22–0.46)	0.13 (0.08–0.20)	0.41 (0.25–0.58)	0.22 (0.13–0.33)
Positive test results, *n*	145	37	69	145	37	69	145	37	69
Negative predictive value									
Value (95% CI)	0.95 (0.92–0.97)	0.92 (0.89–0.95)	0.92 (0.89–0.94)	0.98 (0.97–0.99)	0.97 (0.95–0.99)	0.97 (0.95–0.98)	1.00 (0.99–1.00)	1.00 (0.98–1.00)	0.99 (0.97–1.00)
Negative test results, *n*	428	445	498	428	445	498	428	445	498
Positive likelihood ratio									
Value (95% CI)	3.66 (2.89–4.64)	13.50 (7.28–25.00)	5.15 (3.43–7.74)	3.83 (3.07–4.78)	16.54 (9.66–28.33)	6.77 (4.63–9.90)	4.17 (3.47–5.01)	18.65 (11.97–29.05)	7.22 (4.99–10.46)
Negative likelihood ratio									
Value (95% CI)	0.38 (0.27–0.54)	0.60 (0.49–0.75)	0.64 (0.52–0.78)	0.23 (0.12–0.46)	0.39 (0.25–0.61)	0.45 (0.31–0.66)	0.06 (0.01–0.44)	0.12 (0.03–0.45)	0.32 (0.16–0.62)
Area under ROC curve									
Value (95% CI)	0.81 (0.74–0.88)	0.85 (0.77–0.92)	0.75 (0.68–0.82)	0.87 (0.80–0.92)	0.90 (0.82–0.98)	0.83 (0.74–0.92)	0.96 (0.92–1.00)	0.96 (0.93–0.99)	0.85 (0.74–0.96)
CTC examinations read by all 3 readers		446			446			446	

Sensitivity, per Polyp	Reference Size of Confirmed Polyp								
	≥6 mm			≥8 mm			≥10 mm		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Adenoma or carcinoma									
True-positive results, *n*	62	31	28	34	23	22	18	14	13
False-negative results, *n*	29	41	63	9	12	23	2	3	8
Value (95% CI)	0.68 (0.58–0.78)	0.43 (0.31–0.55)	0.31 (0.22–0.41)	0.79 (0.64–0.90)	0.66 (0.50–0.81)	0.49 (0.34–0.64)	0.90 (0.68–0.99)	0.82 (0.57–0.96)	0.62 (0.38–0.82)
Lesions, *n*	91	72	91	43	35	45	20	17	21
Lesions, any histology									
True-positive results, *n*	107	44	39	43	29	28	19	16	17
False-negative results, *n*	69	100	135	29	30	44	15	13	19
Value (95% CI)	0.61 (0.53–0.68)	0.31 (0.23–0.39)	0.22 (0.16–0.29)	0.60 (0.48–0.71)	0.49 (0.36–0.63)	0.39 (0.28–0.51)	0.56 (0.38–0.73)	0.55 (0.36–0.74)	0.47 (0.30–0.65)
Lesions, *n*	176	144	174	72	59	72	34	29	36

CTC = computed tomographic colonography; OC = optical colonoscopy; ROC = receiver-operating characteristic.

* Sensitivity refers to the fraction of participants with confirmed lesions (of the specified size) that were prospectively identified by each CTC reader. Specificity refers to the fraction of participants without confirmed lesions similarly categorized prospectively by CTC readers. Positive predictive value is the fraction of participants with CTC findings (of the specified size) also confirmed by the reference standard. Negative predictive value is the fraction of participants without lesions of the specified size detected on CTC who also had no lesions confirmed by the reference standard. The ROC curve plots sensitivity versus the false-positive rate and the area under the ROC curve indicates the accuracy of CTC. To permit interobserver comparisons, in this table we calculated the ROC data by using matched cases read by all 3 readers. CTC interpretations were deemed positive for prospective identification of lesions ≥6 mm.