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SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Accuracy of First- and Second-Generation Colon Capsules in Endoscopic Detection of Colorectal Polyps: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: **Colon capsule endoscopy (CCE) is a noninvasive technique used to explore the colon without sedation or air insufflation. A second-generation capsule was recently developed to improve accuracy of detection, and clinical use has expanded globally. We performed a systematic review and meta-analysis to assess the accuracy of CCE in detecting colorectal polyps.**

METHODS: **We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and other databases from 1966 through 2015 for studies that compared accuracy of colonoscopy with histologic evaluation with CCE. The risk of bias within each study was ascertained according to Quality Assessment of Diagnostic Accuracy in Systematic Reviews recommendations. Per-patient accuracy values were calculated for polyps, overall and for first-generation (CCE-1) and second-generation (CCE-2) capsules. We analyzed data by using forest plots, the I^2 statistic to calculate heterogeneity, and meta-regression analyses.**

RESULTS: **Fourteen studies provided data from 2420 patients (1128 for CCE-1 and 1292 for CCE-2). CCE-2 and CCE-1 detected polyps >6 mm with 86% sensitivity (95% confidence interval [CI], 82%–89%) and 58% sensitivity (95% CI, 44%–70%), respectively, and 88.1% specificity (95% CI, 74.2%–95.0%) and 85.7% specificity (95% CI, 80.2%–90.0%), respectively. CCE-2 and CCE-1 detected polyps >10 mm with 87% sensitivity (95% CI, 81%–91%) and 54% sensitivity (95% CI, 29%–77%), respectively, and 95.3% specificity (95% CI, 91.5%–97.5%) and 97.4% specificity (95% CI, 96.0%–98.3%), respectively. CCE-2 identified all 11 invasive cancers detected by colonoscopy.**

CONCLUSIONS: **The sensitivity in detection of polyps >6 mm and >10 mm increased substantially between development of first-generation and second-generation colon capsules. High specificity values for detection of polyps by CCE-2 seem to be achievable with a 10-mm cutoff and in a screening setting.**

Keywords: Imaging; PillCam; Colorectal Cancer Screening; Colorectal Cancer.

Abbreviations used in this paper: **AUC, area under the curve; CCE, colon capsule endoscopy; CI, confidence interval; CRC, colorectal cancer; DOR, diagnostic odds ratio; FDA, Food and Drug Administration; FOBT, fecal occult blood test; LR, likelihood ratio; MeSH, medical subject headings; NLR, negative likelihood ratio; PEG, polyethylene glycol; PLR, positive likelihood ratio; PMDA, Pharmaceuticals and Medical Device Agency; QUADAS, Quality Assessment of Diagnostic Accuracy in Systematic Reviews; SROC, summary receiver operating characteristic curve.**

Most current article

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Colon capsule endoscopy (CCE), introduced in 2006, has generated great expectations,[1] but the enthusiasm for this new, noninvasive technique able to explore the colon without sedation and air insufflation was mitigated when the first studies were published.[2,3] Compared with colonoscopy, the first generation of CCE was shown to be a feasible and safe imaging test of the colon. However, sensitivity for clinically meaningful lesions, ie, ≥6 mm polyps or masses, appeared to be suboptimal.[2–4] For this reason, a second-generation capsule (CCE-2) was developed.[5,6] New technology was implemented; in particular, the capsule frame rate increased from 4 to 35 images per second to adequately image the mucosa when the capsule is accelerated by peristalsis. The angle of view also increased from 156° to 172° for each lens to cover nearly 360° of the colon surface. The Data Recorder (DR3) was also improved by simplifying the procedure.

For both generation capsules, ambitious claims mostly are based on relatively few within-subject comparisons with colonoscopy from single centers.[7] These studies vary considerably in terms of study design, selected population, and technical performances of the colon capsule. Moreover, although the second generation is believed to have higher accuracy when compared with the first generation of colon capsule, this assumption was never systematically demonstrated.

A core body of evidence now exists for CCE-2, including pivotal trials in the United States and Japan that were recently published.[8,9] These trials prompted the U.S. Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Device Agency (PMDA) to recently clear the device for use in these countries. Furthermore, in 2016 the FDA further expanded the indication for the second-generation capsule. Performing a meta-analysis is necessary to more thoroughly understand the performance of CCE-2 across varied studies and assess its differences from the older and underperforming CCE-1, where misconceptions may still reside around the accuracy of the first versus second generation.

The aim of this systematic review and meta-analysis was to assess CCE accuracy as verified with within-subjects colonoscopy in detecting colorectal lesions and to compare the performance of the first and second generations of colon capsule.

Methods

Methods of analysis and inclusion criteria were based on PRISMA recommendations.[10]

Eligibility Criteria

We considered all clinical studies (involving human subjects) from 1966 to September 15, 2015, in which accuracy of CCE for colorectal polyps was assessed by using colonoscopy with histology as comparator. Animal and review studies were excluded. If there was any suspicion of cohort overlap between studies, only the most recent study was included.

Information Sources

Relevant original publications (in English language) were identified in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials and in the abstract publications of the largest medical conferences on this topic (Digestive Disease Week and United European Gastrointestinal Week). Prespecified Medical Subject Headings (MeSH) and non-MeSH terms were used for the search and are reported in Supplementary Material. Both full texts and abstracts were included. Abstracts were included to minimize publication bias. Additional publications were identified through searching the reference lists of retrieved articles. A full list of retrieved studies and the reason for exclusion are in Supplementary Table 1. When further information from selected articles was needed to clarify methodology/data of included studies, we attempted to contact the authors (Supplementary Table 2).

Study Selection

All titles and abstracts of articles retrieved in the prespecified search were independently screened by 2 reviewers (C.H., C.S.). By using the full report of the study, studies were evaluated for inclusion in the analysis. The following inclusion criteria were applied: (1) use of colon capsule, (2) detection of polyps/neoplasia as study end point, (3) colonoscopy with histology used as reference standard, and (4) possibility to extract data from 2 × 2 tables to define CCE accuracy. Exclusion criteria were (1) inflammatory bowel disease–related CCE study with end points other than sporadic neoplasia, (2) suboptimal reference standard such as computed tomography colonography or fecal tests, and (3) poor quality of data preventing an adequate extraction. Any disagreements were resolved through consensus. Data were extracted from the included studies by 1 reviewer (C.S.) and checked by 1 of the second reviewers (C.H., J.A.L., R.P., S.A.G., F.S.S.), and the data were extracted into tables. Any disagreements were resolved through discussion with a third reviewer (S.P.).

Data Collection Process and List of Items

From each article, the reviewers independently abstracted the following information: (1) year of publication; 2) type of publication (full text/abstract); 3) country(ies); (4) number of centers; (5) study design (prospective/retrospective/mono-/multi-center); (6) generation of CCE (1 vs 2); (7) polyethylene glycol (PEG) volume administered; (8) type and volume of booster; (9) matching rule between CCE and colonoscopy adopted (if any); (10) availability of either or both per-patient and per-polyp analysis; (11) timing of colonoscopy (same day

as CCE vs different day); (12) unblinding of CCE results at colonoscopy; (13) number of patients enrolled/included; (14) reasons for exclusion; (15) mean age and (16) indications (colorectal cancer [CRC] screening, family/personal history of colorectal neoplasia, symptoms, positive fecal occult blood test [FOBT], positive imaging tests, other); (17) rate of adequate cleansing at CCE; (18) CCE excretion rates at different timings (<8 hours, 8–10 hours, >10 hours); (19) colon transit time (minutes) (mean/median); (20) number of patients with any polyp size or (21) ≥6 mm/≥10 mm polyps at CCE and colonoscopy; (22) number of patients with at least 1 adenoma of any size or (23) ≥6 mm/≥10 mm at CCE and colonoscopy; (24) number of patients with at least 1 sessile serrated polyp of any size or (25) ≥6 mm/≥10 mm at CCE and colonoscopy; (26) number of patients with at least 1 invasive CRC at CCE and colonoscopy; and (27) rate of adverse events at CCE and colonoscopy.

Risk of Bias in Individual Studies

To assess the methodological quality of the included studies and detect potential bias, the Quality Assessment of Diagnostic Accuracy in Systematic Reviews (QUADAS) was used.[11]

Summary Measures

The primary end points of this systematic review were (1) the per-patient sensitivity of CCE for different categories of polyp size (≥6 vs ≥10 mm) and (2) the per-patient sensitivity of CCE for cancer.

Data and Statistical Analysis

The standard methods recommended for the diagnostic accuracy of meta-analyses were used.[12] The following measures of test accuracy for different polyps sizes were computed for each individual study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). The diagnostic threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve.[13] The area under the curve (AUC) was calculated. The AUC is a measure of the ability to discriminate between those with and without disease. A value of 0.5 is no better than chance, whereas a value of 1.0 represents perfect diagnostic test discrimination; tests with values greater than 0.80 are generally considered to have good discerning properties. The inter-study heterogeneity was calculated by the χ^2-based Q test and the inconsistency index I^2. When a significant Q test ($P < .05$ or $I^2 > 50\%$) indicated heterogeneity among studies, the random-effects model (DerSimonian–Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, and other related indexes of the studies; otherwise, the fixed-effects model (Mantel–Haenszel method) was chosen. As a further assessment of threshold effect, we also calculated the Spearman correlation coefficient between sensitivity (logit of the true-positive rate) and specificity (logit of the false-positive rate) for each test. If threshold effect exists, an inverse correlation appears. We considered a positive Spearman correlation coefficient of >0.6 to be strong and suggestive of threshold effect.[13,14] If the value was less than 0.6, the accuracy of the tests could be based on pooled estimates of sensitivity and specificity.

Meta-regression was performed to investigate the source of heterogeneity within the included studies (inverse variance weighted). Subgroup analyses were also performed if necessary to dissect the heterogeneity. Because publication bias is of concern for meta-analyses of diagnostic studies, we tested for the potential presence of this bias by using Deeks' funnel plots. Analyses were performed by using R software 2.15.2 (2012-10-26).[15] R Foundation for Statistical Computing, Vienna, Austria. In every test, a two-sided P value <.05 was considered statistically significant.

Results

Study Selection and Characteristics of Included Studies

The study flow chart is shown in Figure 1; 14 studies were included in the analysis. To obtain further information, 2 authors were contacted (Supplementary Table 2). Main characteristics of the included studies are provided in Supplementary Tables 3 and 4.

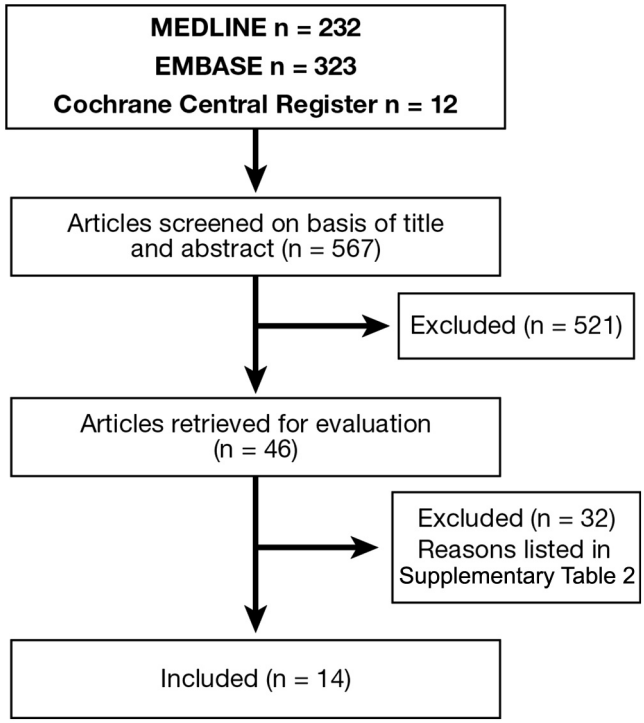

Figure 1. Flow chart of the systematic review.

Participants

The studies, performed between 2006 and 2015, varied in patient accrual from 40 to 884, with a median of 79 participants per series (interquartile range, 59–198) (Supplementary Table 4). Overall, the total number of enrolled patients was 2681, but 261 (9.7%) were excluded from the original trials (mean of patients excluded per trial, 19; median, 6; range, 0–189). Thus, in the final analysis, we included 14 studies with a total of 2420 participants. Across the 14 eligible studies, the indications for endoscopy included CRC screening (n = 1261, 47%), post-polypectomy surveillance or CRC family history (636, 24%), FOBT positivity and/or symptoms (619, 23%), positive imaging tests (136, 5%), and other indication (24, 1%).

Interventions

Capsule generation. Seven studies (involving 1128 patients) tested the accuracy of CCE-1, and the remaining 7 series (1292 patients) used CCE-2 (Supplementary Table 5).

Bowel preparation and excretion. Capsule bowel preparation and excretion rates are described in Supplementary Table 5. The median rates of adequate cleansing level were 78% and 81% with CCE-1 and CCE-2 studies, respectively. The type of capsule did not significantly affect the excretion rate (86.7%; 95% confidence interval [CI], 79.3%–91.7% for CCE-1 vs 90.5%; 95% CI, 88.3%–92.4% for CCE-2; $P = .203$).

Outcomes

Prevalence of patients with at least one ≥6 mm polyp at colonoscopy was reported in 13 series including 2358 patients, and the cumulative prevalence was 24.7% (583 of 2358). Prevalence of patients with at least one ≥10 mm polyp was reported in 8 series (2095 patients), and the cumulative prevalence was 12.7% (281 of 2204).

Risk of Bias Within Studies

Quality assessment of the individual studies is reported in Supplementary Table 6. Patients were recruited consecutively in 2 studies, whereas in the others a nonconsecutive recruitment prevented a reliable assessment of the withdrawal rate. Only 2 trials included asymptomatic subjects (1109 patients, 41.4% of the total) who may be considered as typically representative of a CRC screening population,[8,16] whereas the remaining 12 studies enrolled a symptomatic and/or disease-enriched population. Colonoscopy was performed in all the studies after CCE, with the endoscopist blinded to CCE results. This was mainly due to the difficulty of reading CCE examinations before the performance of colonoscopy, with 2 exceptions where unblinding was performed after cecal intubation or colonoscopy. For this reason, eventual false negatives at colonoscopy were generally classified as false positives at CCE, presumably underestimating CCE accuracy. To assess CCE accuracy on the basis of colonoscopy results, a matching-polyp algorithm between CCE and colonoscopy results is required.

Synthesis of Results

Diagnostic accuracy analysis: ≥6 mm polyps. Per-patient data for ≥6 mm polyps could be obtained in 13 of the 14 trials (2358 participants). The sensitivity and specificity of CCE to detect patients with ≥6 mm polyps are shown in a forest plot (Figure 2*A*) and in Supplementary Table 7. There was substantial between-study heterogeneity for both sensitivity ($I^2 = 86.1\%$; 95% CI, 78%–91%; $P < .0001$) and specificity ($I^2 = 85.8\%$; 95% CI, 77.3%–91.1%; $P < .0001$). For full details and the SROC curve, see Supplementary Material and Supplementary Figure 1, respectively. Significant values for study heterogeneity were mainly caused by 1 study[16] that was atypical in respect to sensitivity. In a sensitivity analysis (Supplementary Material and Supplementary Figure 2), this trial was identified as an outlier. Removal of this study reduced the amount of heterogeneity from 86.1% to 31.5% ($P = .109$).

Diagnostic accuracy analysis: ≥10 mm polyps. Per-patient data for ≥10 mm polyps could be obtained in 10 of the 14 trials. Figure 2*B* displays the forest plots of the sensitivity and specificity of CCE in these 10 studies for the detection of ≥10 mm polyps. The I^2 of sensitivity and specificity were 53.4% ($P < .001$) and 31.3% ($P = .002$), respectively. The pooled estimated sensitivity and specificity from the random-effects model were 81.0% (95% CI, 66.0%–90.3%) and 96.2% (95% CI, 94.0%–97.6%), respectively. The pooled PLR, NLR, and DOR were 18.6 (95% CI, 12.0-28.2), 0.22 (95% CI, 0.13–0.34), and 90.4 (95% CI, 44–163), respectively. Our data showed that the SROC curve for detecting ≥10 mm polyps is positioned near the desirable upper left corner, and the AUC was 0.94 (95% CI, 0.88–1.00), indicating that the level of overall accuracy was high. Heterogeneity was mainly caused by one large study that was atypical with respect to sensitivity.[17]

Meta-regression analysis: diagnostic performance of test for detecting ≥6 mm polyps. Because significant heterogeneity was identified among included studies, a meta-regression analysis was performed to explore the possible covariates for the heterogeneity. The covariates selected in the present meta-regression were geographical location (Europe compared with Asia/United States), sample size, study design (multicenter compared with single center), mean age of participants, study population (only asymptomatic people vs high-risk or symptomatic subjects), and type of CCE (second vs first generation). The outcomes of meta-regression are shown in Table 1.

Meta-regression including sample size, mean age, geographical location, and study design did not yield any

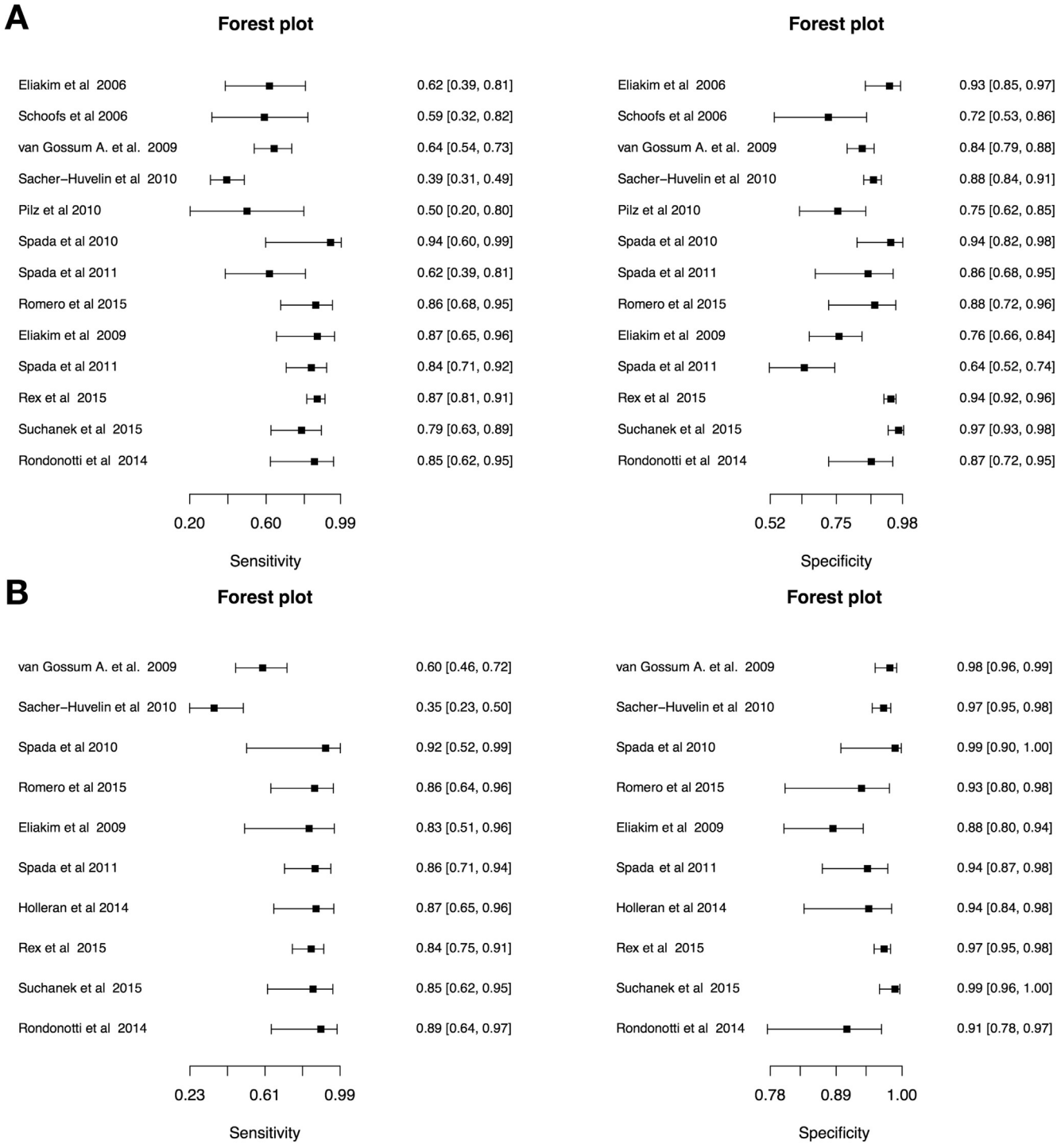

Figure 2. Forest plots show per-patient sensitivity and specificity of CCE to detect ≥6 mm polyps (*A*) and ≥10 mm polyps (*B*) with 95% CI for each individual study. In these graphs, between-study variability is also provided, showing substantial heterogeneity for sensitivity for both ≥6 mm (*A*) and ≥10 mm polyps (*B*).

significant results. According to meta-regression analysis, the earlier a study had been performed, the lower was the performance of CCE; the sensitivity of CCE in detecting clinically significant polyps (≥6 mm in size) increased by increasing year of publication (regression coefficient, 0.16; 95% CI, 0.02–0.30; $P = .021$), whereas false-positive rate decreased (regression coefficient, –0.13; 95% CI, –0.26 to 0.01; $P = .078$). CCE showed better specificity in studies including only asymptomatic subjects: regression coefficient for false-positive rate, –1.5; 95% CI, –2.3 to –0.7; $P < .001$). Interestingly, the point estimate for the sensitivity did not indicate any significant effect (regression coefficient, 0.821; 95% CI, –0.266 to 1.91; $P = .139$). Compared with CCE-1, there was increased sensitivity for detection of polyps ≥6 mm (regression coefficient, 1.48; 95% CI, 0.89–2.08;

Table 1. Univariate Meta-regression With Random-effects Model of Logit of Observed True-positive (Polyps ≥6 mm) and False-positive Rates to Sociodemographic, Methodological, and Clinical Characteristic

Variable	Coefficient (sensitivity) (95% CI)	*P* value	Coefficient (false-positive rate) (95% CI)	*P* value
Sample size (no. of participants, as continuous variable)	−0.0 (−0.003 to 0.002)	.757	0.001 (−0.15 to 0.001)	.165
Year of the study				
as continuous variable (in years)	0.16 (0.02–0.30)	.021	−0.13 (−0.25 to 0.01)	.078
as categorical (2011 or after vs before 2011)	1.10 (0.34–1.2)	.004	−0.4 (−1.3 to 0.5)	.419
Geographical location (Europe vs Asia/USA)	−0.588 (−1.697 to 0.521)	.299	0.395 (−0.685 to .0.521)	.474
Study design (multicenter vs single center trial)	0.164 (−0.91 to 1.23)	.765	−0.511 (−1.475 to 0.452)	.298
Study population (asymptomatic vs symptomatic and/or disease-enriched population)	0.821 (−0.266 to 1.908)	.139	−1.471 (−2.250 to −0.692)	<.001
CCE type (second vs first generation)	1.49 (0.89–2.08)	<.001	−0.14 (−1.1 to 0.81)	.776
Mean age of participants as continuous variable (years)	−0.089 (−0.261 to 0.082)	.307	−0.019 (−0.166 to 0.128)	.800

$P < .001$) and no difference in specificity (regression coefficient, –0.14; 95% CI, –1.1 to 0.90; $P = .776$) with second-generation systems. Finally, multivariate analysis that was based on type of systems, disease prevalence, and year of study publication was also performed. In the multivariate analysis, disease prevalence remained significantly associated with test specificity (regression coefficient for false positivity rate, –1.4; 95% CI, –2.5 to 0.28; $P = .015$) and CCE type with test sensitivity (regression coefficient for sensitivity, 1.6; 95% CI, 0.7–2.6; $P = .001$).

To confirm results of meta-regression, 2 subgroup analyses were performed. As shown in Figure 3*A*, the test sensitivity for ≥6 mm polyps in studies that used CCE-2 was 86% (95% CI, 82%–89%) ($I^2 = 0\%$; $P = .896$), whereas the sensitivity in studies that used CCE-1 was 58% (95% CI, 44%–70%) ($I^2 = 65.0\%$; $P = .009$). The overall specificities of CCE-2 and CCE-1 were similar: 88.1% (95% CI, 74.2%–95.0%) vs 85.7% (95% CI, 80.2%–90.0%) ($P = .695$). The pooled PLR, NLR, and DOR for CCE-2 were 7.9 (95% CI, 3.7–16.1), 0.16 (95% CI, 0.12–0.21), and 50.5 (95% CI, 20.3–107.0), respectively. The corresponding figures for CCE-1 were 3.7 (95% CI, 3.0–4.4), 0.51 (95% CI, 0.40–0.64), and 7.4 (95% CI, 5.0–10.4). Specificity of CCE was influenced by the prevalence of disease; the overall specificity of CCE was 94.7% (95% CI, 91.0%–96.1%) among asymptomatic subjects (2 trials, n = 920), and it was 83.7% (95% CI, 81.0%–85.7%) among high-risk/symptomatic patients ($P < .001$) (Figure 4). The pooled PLR, NLR, and DOR in the asymptomatic subjects were 18.7 (95% CI, 10.3–31.8), 0.17 (95% CI, 0.10–0.26), and 113 (95% CI, 63.6–182), respectively. The corresponding figures for disease-enriched populations were 4.0 (95% CI, 3.0–5.2), 0.4 (95% CI, 0.3–0.5), and 10.7 (95% CI, 6.4–16.6), respectively.

Meta-regression analysis: diagnostic performance of test for detecting ≥10 mm polyps. According to meta-regression analysis, sensitivity for detecting ≥10 mm polyps differed according to the generation of CCE (regression coefficient, 1.7; 95% CI, 1.0–2.5; $P < .001$) (Figure 3*B*). The effect on specificity was not significant (regression coefficient, 0.85; 95% CI, –0.16 to 1.9; $P = .100$). Specificity among studies assessing only asymptomatic populations was higher than that among studies assessing disease-enriched populations (regression coefficient, –0.88, 95% CI, –1.9 to 0.09; $P = .075$), whereas sensitivity was similar (regression coefficient, 0.4; 95% CI, –1.3 to 1.9; $P = .664$). Also, sensitivity of CCE tended to change with year of publication (coefficient regression, 0.21; 95% CI, –0.02 to 0.45; $P = .069$). Estimates were consistent with results of subgroup analyses. Sensitivity and specificity for CCE-2 were 87% (95% CI, 81%–91%; $I^2 = 0\%$; $P = .994$) and 95.3% (95% CI, 91.5%–97.5%; $I^2 = 67.0\%$; $P = .006$), respectively, and 54% (95% CI, 29%–77%; $I^2 = 76.2\%$; $P = .015$) and 97.4% (95% CI, 96.0%–98.3%; $I^2 = 0\%$; $P = .543$) for CCE-1, respectively. The overall specificity was 98% (95% CI, 94%–99%; $I^2 = 56.5\%$; $P = .364$) for the subgroup of studies assessing asymptomatic individuals, and it was 95% (95% CI, 91.0%–97.0%; $I^2 = 59.5\%$; $P = .014$) for those including also high-risk/symptomatic patients ($P = .080$). Multivariate analysis, which was based on year of publication, disease prevalence, and system type, indicated that the association between CCE type and test sensitivity (regression coefficient, 1.8; 95% CI, 0.88–2.7; $P < .001$) and that between disease prevalence and specificity (regression coefficient, –1.3; 95% CI, –1.9 to –0.6; $P = .004$) were statistically significant.

Histology

Insufficient studies reported on the histology of ≥6 mm and ≥10 mm polyps to warrant assessment in the meta-analysis. This prevented separate subanalysis according to polyp histology (ie, adenomas, serrated, etc).

Cancer

Of the 14 trials, 10 provided data about cancer detection. There were no missed cancers (n = 11) in series where CCE-2 was used (cumulative per-patient

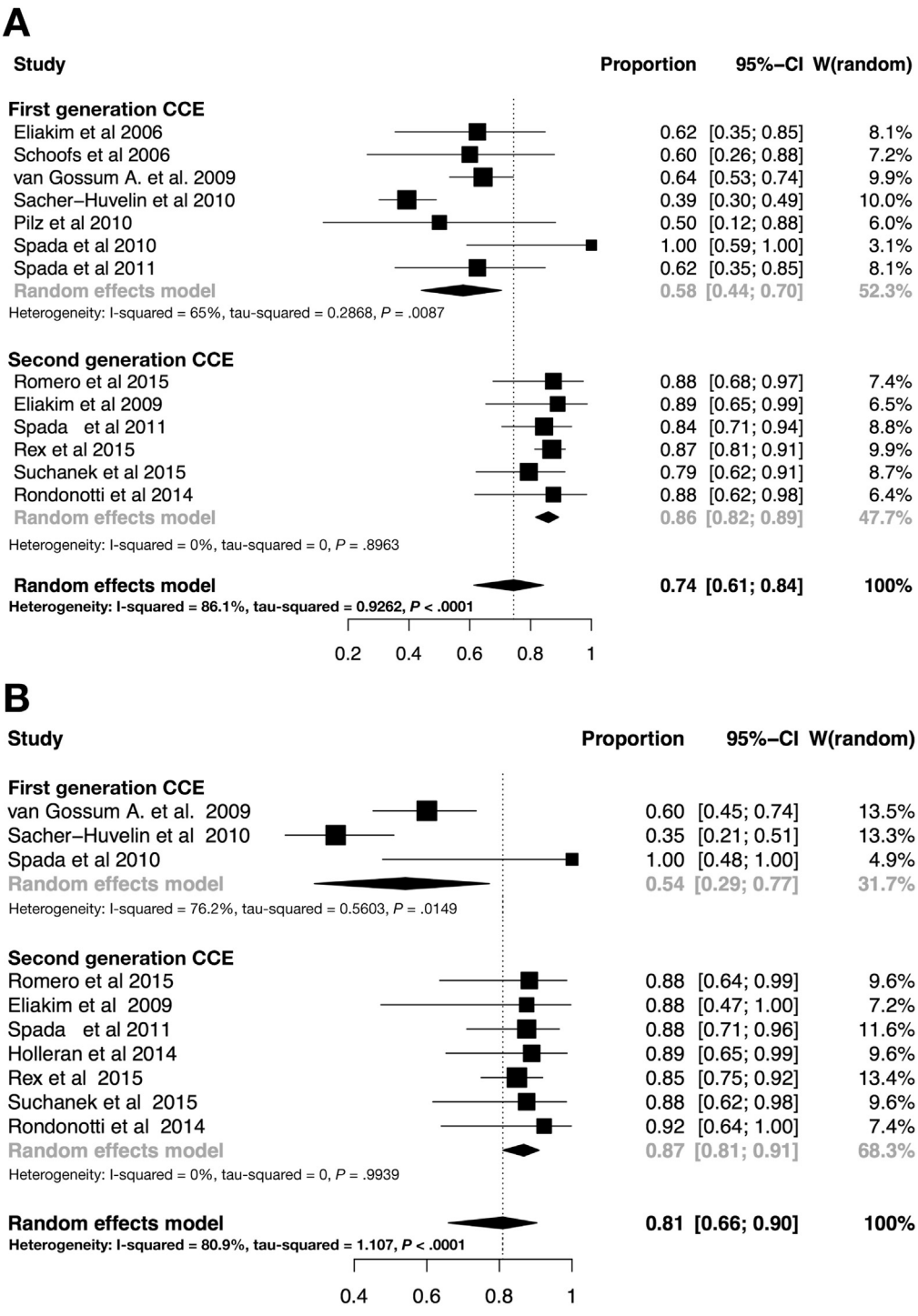

Figure 3. Subgroup analysis: sensitivity of second- vs first-generation systems for polyps ≥6 mm (*A*) and ≥10 mm (*B*). Events, TPs ([true positives], ie, patients with polyps ≥6 mm [*A*] or ≥10 mm [*B*]) found at CCE; Total, TPs at the reference standard (colonoscopy). Proportion, percentage of TPs found at CCE among patients with endoscopically proven polyps ≥6 mm (*A*) or ≥10 mm (*B*).

sensitivity, 100%), whereas 6 of the 26 proven cancers were missed in series that used CCE-1 (cumulative sensitivity, 77%; $P = .349$).

Publication Bias Evaluation

Evaluation by both Egger's test ($P = .652$) and Begg's test ($P = .693$) did not show evidence of publication bias for log DOR. This result was confirmed by inspection of the funnel plots, which were all symmetrical for the investigated diagnostic measures (sensitivity, specificity, positive predictive value, negative predictive value, likehood ratio (LR)+, LR− data not shown and accuracy; Figure 5).

Adverse Events

Overall, 245 adverse events were reported in 13 of the 14 included trials in 2367 patients, corresponding to a cumulative rate of 10.4%. Of these 245 adverse events,

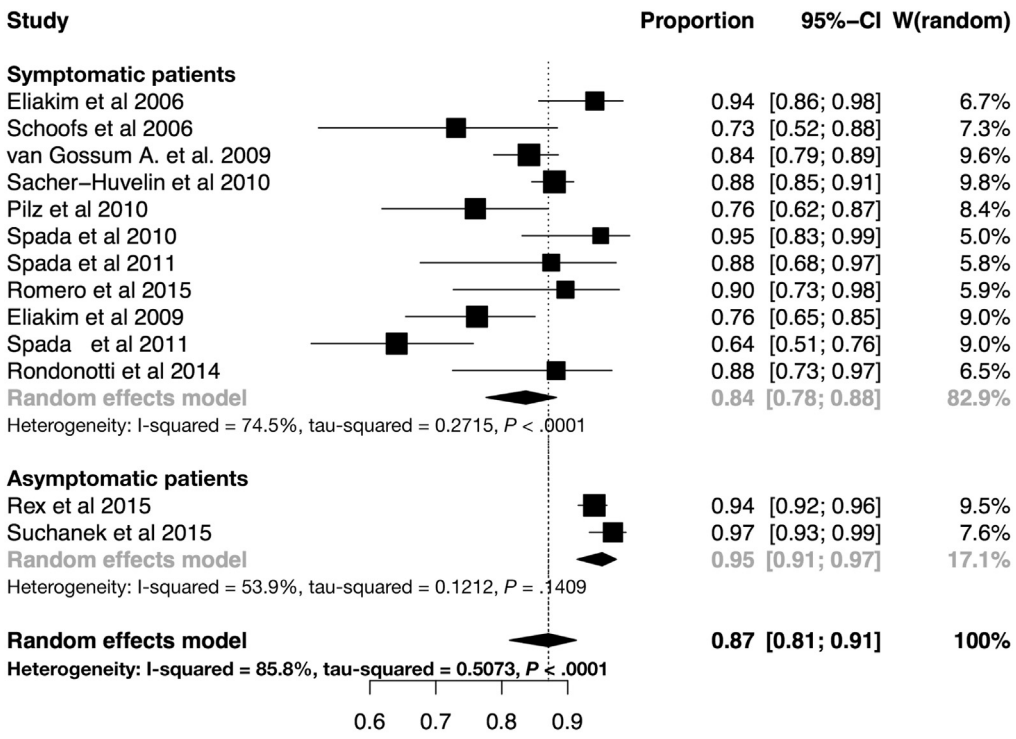

Figure 4. Subgroup analysis: specificity for detecting polyps 6 mm or larger among series involving only asymptomatic subjects vs enriched-disease population. Events, TNs ([true negatives], ie, patients without polyps ≥6 mm) found at CCE; Total, TNs at the reference standard (colonoscopy). Proportion, percentage of TNs found at CCE among patients without endoscopically proven polyps ≥6 mm.

208 occurred in 2142 patients related to bowel preparation (cumulative rate, 208 of 2142; 9.7%). Data on the adverse events related to CCE or CC were available in 12 of 13 trials including 1822 patients. There were 6 adverse events in these 1822 patients related to the capsule, yielding a cumulative rate of 0.33%. There were 20 adverse events related to colonoscopy in 12 of 14 studies in 2047 patients, corresponding to a cumulative rate of 0.98%. Most adverse events appeared to be mild/moderate (ie, nausea, vomiting, abdominal pain), with the exception of 6 cases that were related to colonoscopy and/or polypectomy: colonic perforation (n = 3), post-polypectomy bleeding (n = 2), and cardiac failure (n = 1). None of the 6 CCE-related adverse events was severe.

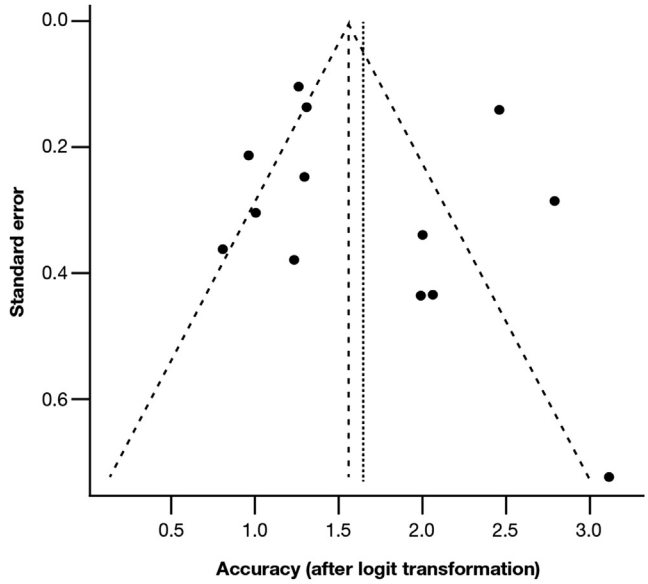

Figure 5. Funnel plot for CCE accuracy (after logit transformation) of individual trials against their standard errors.

Discussion

There is now a core body of literature for CCE, with the recent publication of second-generation pivotal trials in the United States and Japan.[8,9] This is resulting in global expansion of device acceptance, including FDA and PMDA clearance, and a new user base. Understanding the performance of CCE-2 across varied studies and the differences from CCE-1 was assessed herein, which is critical in this changing and growing CCE environment and will help to guide practitioners regarding device usage. According to our per-patient analysis that used colonoscopy as the gold standard, CCE-2 sensitivity for both ≥6 mm and ≥10 mm polyps was adequate and was substantially improved as compared with CCE-1. We also showed that CCE specificity was higher for ≥10 mm vs ≥6 mm polyps and higher for CRC screening, compared with disease-enriched populations.

The results of our meta-analysis are relevant for the following reasons. First, the sensitivity values achieved by CCE-2, ie, 86% and 87% for ≥6 mm and ≥10 mm polyps, represent a clinically relevant improvement compared with the corresponding values shown by CCE-1, ie, 58% and 54% for ≥6 mm and ≥10 mm polyps. Although the >85% sensitivity of CCE-2 may be considered clinically adequate for a noninvasive screening or diagnostic test because it is equal or superior to that of computed tomography colonography,[18] the <70% sensitivity shown by CCE-1 is regarded as

suboptimal. The relatively high sensitivity of CCE-2 for ≥6 and ≥10 mm polyps is clinically strengthened by the 100% detection of the 11 invasive carcinomas present in the included series.

Second, the association between polyp size and CCE specificity is clinically relevant. The increase in positive LR from 5.6 to 18.6 with an increase from a 6-mm to a 10-mm cutoff may be useful to reduce the rate of post-CCE colonoscopies. This is in line with the 10-mm cutoff adopted in pragmatic trials of computed tomography colonography.[19,20] The fact that most advanced colorectal neoplasia is actually harbored in ≥10 mm rather than in ≥6 mm polyps would further support the adoption of such a cutoff in clinical practice.[21]

Third, when considering that clinical importance of specificity is inversely related with prevalence of disease, the higher CCE specificity in screening asymptomatic subjects as compared with disease-enriched populations is clinically reassuring. One possible explanation is the overcalling of findings in disease-enriched populations vs the screening setting. Furthermore, unblinding of CCE results before colonoscopy was performed in a large screening trial, which may have improved the specificity in this population.[8] Overall, our estimates of specificity and positive LRs are likely to represent a worst-case scenario for CCE, because post-CCE colonoscopy was performed in most of the studies without unblinding of CCE results. It is possible that a false-negative colonoscopy may have been incorrectly classified as a false-positive CCE, artificially worsening CCE specificity. The higher specificity of CCE for ≥10 mm as compared with ≥6 mm lesions would support this argument, when considering the association between missed lesions at colonoscopy and polyp size in tandem colonoscopy studies.[22,23]

The main strength of our analysis is that colonoscopy with histology was the gold standard in all series. Despite the fact that colonoscopy is hampered by a significant miss rate, especially for 6–9 mm polyps,[22,23] it remains the most accurate diagnostic technique available for colorectal polyps. The main limitation of our meta-analysis is represented by the high level of heterogeneity present in our estimates. However, we were able to identify one article with atypical estimates that was mainly responsible for such heterogeneity.[17] Fortunately, there was no heterogeneity in the accuracy of CCE-2 for ≥6 mm and ≥10 mm polyps. Second, our estimates that were based on polyp detection may be only considered as a proxy for neoplasia detection. However, this is inherent in any noninvasive test that does not allow for biopsies, such as CCE and computed tomography colonography.[24] Third, the design of our analysis excluded the assessment of CCE uptake from general or clinical populations, as other studies did.[25,26] However, accuracy values are independent from uptake values.

Colonoscopy remains the gold standard for CRC screening. Although CCE-2 had good accuracy, in particular for the screening population and polyps ≥10 mm, the device remains somewhat less sensitive than colonoscopy for the detection of clinically significant polyps. The ~95% specificity of CCE-2 for large polyps and asymptomatic individuals appears largely equivalent to that of colonoscopy, although it was lower in the diagnostic population for polyps ≥6 mm. The 81% rate of adequate cleansing for CCE-2 was lower than would be expected with colonoscopy, likely in part related to the inability of the capsule to irrigate. Similarly, the exam completion rate was 90.5%; again this is somewhat lower than the cecal intubation rate expected for colonoscopy. The results of this analysis also showed that CCE is an extremely safe procedure, with no serious adverse events in more than 2000 patients, which may be a competitive advantage over colonoscopy.[27]

In comparison with colonoscopy, CCE-2 has both advantages and disadvantages. In general, colonoscopy remains superior to CCE-2 for several reasons. It has the ability for intervention, whereas CCE is a diagnostic modality; there is some uncertainty related to the most appropriate polyp size cutoff for referral to colonoscopy after positive CCE; 2 recent publications raised uncertainty regarding CCE-2 accuracy for sessile serrated polyps, with the larger trial showing a low sensitivity and the other suggesting robust detection[8,9]; the bowel prep is slightly more aggressive for CCE-2 vs colonoscopy, and the capsule cannot remedy substandard bowel preparation through irrigation; and the completion rate is somewhat lower for CCE. Advantages of CCE-2 include its noninvasive and safe nature, absence of sedation, the potential to be appealing to a subset of patients who might not otherwise consider screening, and the ability for patients to perform many normal daily activities while undergoing colonic evaluation. For these reasons, it logically holds that the use of CCE-2 would be most suitable in those who are unwilling to undergo colonoscopy or in whom colonoscopy is not feasible.

In conclusion, our study showed adequate detection of both ≥6 mm and ≥10 mm colorectal polyps by CCE-2 was significantly improved vs CCE-1. When coupled with its safety profile, the colon capsule may be a suitable alternative to colonoscopy for colon polyp and CRC screening and diagnosis, particularly in patients unwilling to undertake colonoscopy or for those in whom it is technically not feasible.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.04.038.

References

1. Adler DG, Chand B, Conway JD, et al. Capsule endoscopy of the colon. Gastrointest Endosc 2008;68:621–623.

2. Spada C, Hassan C, Marmo R, et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clin Gastroenterol Hepatol 2010;8:516–522.
3. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009;361:264–270.
4. Eliakim R, Fireman Z, Gralnek IM, et al. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy 2006;38:963–970.
5. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc 2011;74:581–589.e1.
6. Eliakim R, Yassin K, Niv Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy 2009;41:1026–1031.
7. Spada C, Hassan C, Galmiche JP, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2012;44:527–536.
8. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. Gastroenterology 2015;148:948–957.e2.
9. Saito Y, Saito S, Oka S, et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointest Endosc 2015;82:861–869.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–W94.
11. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology 2003;3:25.
12. Jones CM, Ashrafian H, Skapinakis P, et al. Diagnostic accuracy meta-analysis: a review of the basic principles of interpretation and application. Int J Cardiol 2010;140:138–144.
13. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–1316.
14. Colton T. Statistics in medicine. 1st ed. Boston: Little, Brown and Company, 1974.
15. R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Available at: http://www.R-project.org/.
16. Suchanek S, Grega T, Voska M, et al. The efficiency of colonic capsule endoscopy in detection of colorectal polyps and cancers compared to colonoscopy: final results of multicenter, prospective, cross-over study. Gastrointest Endosc 2015;81:AB265.
17. Sacher-Huvelin S, Coron E, Gaudric M, et al. Colon capsule endoscopy vs colonoscopy in patients at average or increased risk of colorectal cancer. Aliment Pharmacol Ther 2010;32:1145–1153.
18. de Haan MC, van Gelder RE, Graser A, et al. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. Eur Radiol 2011;21:1747–1763.
19. Atkin W, Dadswell E, Wooldrage K, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1194–1202.
20. Halligan S, Wooldrage K, Dadswell E, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1185–1193.
21. Hassan C, Pickhardt PJ, Kim DH, et al. Systematic review: distribution of advanced neoplasia according to polyp size at screening colonoscopy. Aliment Pharmacol Ther 2010;31:210–217.
22. Heresbach D, Barrioz T, Lapalus MG, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008;40:284–290.
23. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24–28.
24. Spada C, Hassan C, Barbaro B, et al. Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial. Gut 2015;64:272–281.
25. Adrian-de-Ganzo Z, Alarcon-Fernandez O, Ramos L, et al. Uptake of colon capsule endoscopy vs colonoscopy for screening relatives of patients with colorectal cancer. Clin Gastroenterol Hepatol 2015;13:2293–2301.e1.
26. Spada C, Hassan C, Costamagna G. Colon capsule endoscopy in colorectal cancer screening: a rude awakening from a beautiful dream? Clin Gastroenterol Hepatol 2015;13:2302–2304.
27. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145:880–886.
28. Romero C, Rodriguez de Miguel C, Serradesanferm A, et al. PillCam© colon capsule for colorectal cancer screening: a prospective and comparative study with colonoscopy. Gastroenterology 2015;148:S-759.
29. Holleran G, Leen R, O'Morain C, et al. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy 2014;46:473–478.
30. Schoofs N, Deviere J, Van Gossum A. PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study. Endoscopy 2006;38:971–977.
31. Pilz JB, Portmann S, Peter S, et al. Colon capsule endoscopy compared to conventional colonoscopy under routine screening conditions. BMC Gastroenterol 2010;10:66.
32. Spada C, Hassan C, Ingrosso M, et al. A new regimen of bowel preparation for PillCam colon capsule endoscopy: a pilot study. Dig Liver Dis 2011;43:300–304.
33. Spada C, Riccioni ME, Hassan C, et al. PillCam colon capsule endoscopy: a prospective, randomized trial comparing two regimens of preparation. J Clin Gastroenterol 2011;45:119–124.
34. Rondonotti E, Borghi C, Mandelli G, et al. Accuracy of capsule colonoscopy and computed tomographic colonography in individuals with positive results from the fecal occult blood test. Clin Gastroenterol Hepatol 2014;12:1303–1310.

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Conflicts of interest

These authors disclose the following; Cristiano Spada receives consulting fees from Medtronic. Shabana F. Pasha receives consulting fees from Medtronic and has received research grants from Medtronic and Capsovision and travel grant from Capsovision. Seth A. Gross serves on the advisory panel of Medtronic. Jonathan A. Leighton receives consulting fees from Medtronic and Olympus and received research grants from Medtronic and Capsovision. Felice Schnoll-Sussman serves on the advisory panel of CdX Diagnostics, Interpage Diagnostics, and Medtronic and has served on speakers bureau for Medtronic. Loredana Correale receives consulting fees from Medtronic. Cesare Hassan receives consulting fees from Medtronic. Guido Costamagna receives consulting fees from Medtronic. The remaining author discloses no conflicts.

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Supplementary Material

Medical Subject Headings Terms

("colon"[MeSH Terms] OR "colon"[All Fields] OR "rectum"[MeSH Terms] OR "rectum"[All Fields] OR "colorectal"[All Fields]) AND ("colonic polyps"[MeSH Terms] OR ("colonic"[All Fields] AND "polyps"[All Fields]) OR "colonic polyps"[All Fields] OR ("colon"[All Fields] AND "polyp"[All Fields]) OR "colon polyp"[All Fields] OR "polyps"[MeSH Terms] OR "polyps"[All Fields] OR "polyp"[All Fields] OR "lesion"[All Fields] OR "Adenoma" [Mesh] OR "adenoma"[All Fields] OR "adenomatous"[All Fields] OR "neoplasia"[All Fields] OR "Neoplasms" [Mesh]) AND ("colon capsule endoscopy"[All Fields] OR "capsule endoscopy"[All Fields] OR "Capsule Endoscopy"[Mesh]) AND English[lang].

Per-patient Sensitivity and Specificity for Polyps >5 Millimeters

The Spearman rank correlations between the logistic transformations (logit) of the true-positive rate plotted against the logit of the false-positive rate were −0.038 (95% CI, −0.6 to 0.5), indicating that a threshold effect is unlikely to contribute to heterogeneity. The pooled (random-effects model) estimated sensitivity was 74.4% (95% CI, 61.0%–84.0%), and the pooled specificity was 87.1% (95% CI, 80.3%–91.1%). The I^2 of PLR, NLR, and DOR were 8.9% ($P = .625$), 11.5% ($P = .349$), and 7.9% ($P = .72$), respectively. The overall PLR and NLR were 5.6 (95% CI, 3.6–8.3) and 0.32 (95% CI, 0.22–0.43). The pooled DOR ratio was 18.7 (95% CI, 8.9–35.5). The SROC curve is shown in Supplementary Figure 1, which indicates sensitivity versus 1-specificity (ie, false-positive rate) of individual studies. The area under the SROC curve was 0.87 (95% CI, 0.80–0.94).

Per-patient Sensitivity and Specificity for Polyps >5 Millimeters

The pooled estimated sensitivity and specificity from the random-effects model were 81.0% (95% CI, 66.0%–90.3%) and 96.2% (95% CI, 94.0%–97.6%). The pooled PLR, NLR, and DOR were 18.6 (95% CI, 12.0–28.2), 0.22 (95% CI, 0.13–0.34), and 90.4 (95% CI, 44–163), respectively.

Our data showed that the SROC curve for detecting ≥10 mm polyps is positioned near the desirable upper left corner, and the AUC was 0.94 (95% CI, 0.88–1.00), indicating that the level of overall accuracy was high. Heterogeneity among studies was mainly caused by one large study that was atypical in respect to sensitivity.[16] After this study was removed (in a sensitivity analysis), sensitivity of the test was 84% (95% CI, 74%–91%).

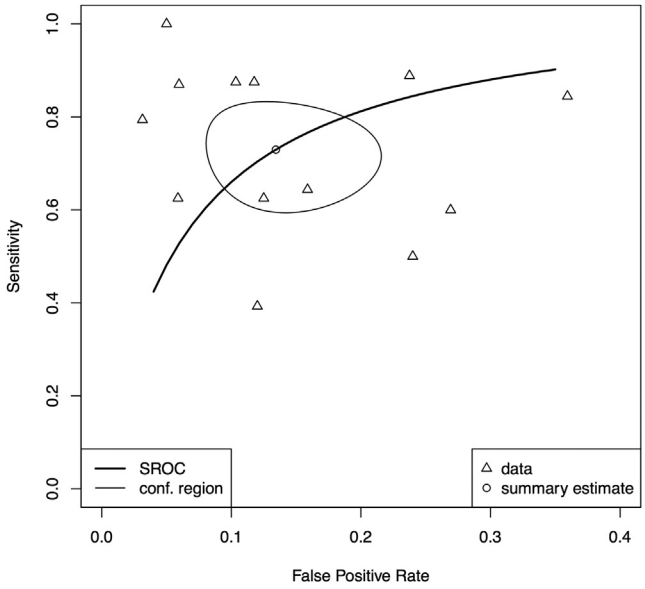
Influence Case Analysis

Methods. An outlying case may not be of much consequence if it exerts little influence on the results. However, if the exclusion of a study from the analysis leads to considerable changes in the model, then the study may be considered to be influential. Case deletion diagnostics known from linear regression (eg, Belsley et al, 1980; Cook and Weisberg, 1982) can be adapted to the context of meta-analysis to identify such studies. The following diagnostic measures for the random-effects model were computed by using R software (Wolfgang Viechtbauer. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 2010;36:1–48.)

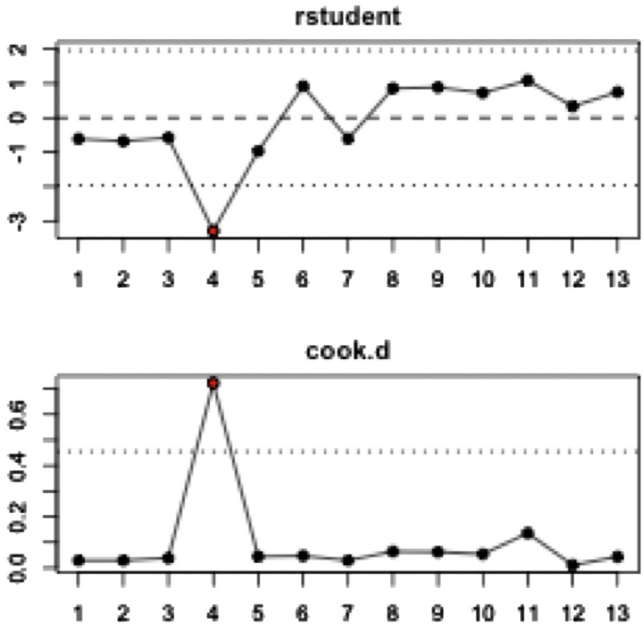
1. Externally standardized residuals
2. Cook's distances
3. the estimates of tau^2 when each study is removed in turn
4. the test statistics for (residual) heterogeneity when each study is removed in turn.

Results. *Influence analysis for the random-effects model: success rate.* The data used in this study were taken from 13 clinical trial articles that investigated diagnostic performance of CCE for detecting clinically significant polyps (6 mm or larger in size). The outcome of this analysis was the sensitivity, ie, the proportion of true-positive patients correctly identified by CCE among positive patients at reference standard.

The results from the random-effects model indicate a significant amount of residual heterogeneity ($I^2 = 86.1\%$; 95% CI, 78.0%–91%; $P < .001$). To detect possible outliers, a variety of outlier and influential case diagnostics were computed (Viechtbauer and Cheung, 2010). Results of the influence analysis are shown in Supplementary Figure 2. On the basis of the Cook's distance (Supplementary Figure 2), we found the following study to be the most influential in the meta-analysis: Sacher-Huvelin et al, 2010. This study was identified as outliers having the highest standardized residuals (Supplementary Figure 2). Removal of this study reduced the amount of heterogeneity from 81.4% to 31.5%. After refitting the model and leaving this study out, the pooled sensitivity was 79.6% (95% CI, 69%–91%).



Supplementary Figure 1. SROC curve is plotted. The summary joint sensitivity and specificity point with confidence region is also plotted: sensitivity, 73%; 95% CI, 62.3%–81.5% and false-positive rate, 0.134; 95% CI, 0.09–0.19). The confidence region is based on the CI around the summary point and indicates that on the basis of the available data, we would expect the "real value" to be within that region 95% of the time.



Supplementary Figure 2. Results of outlier and influence case analysis for random-effects model of CCE sensitivity for clinically significant polyps (≥6 mm). Shown is a plot of standardized residuals (*top*) and Cook's distances (*bottom*) for the random-effects model. Removal of study 4 would reduce the amount of heterogeneity quite a bit and increase the precision of the estimated average outcome from the random-effects model.

Supplementary Table 1. Full Text Retrieved and Reasons for Exclusion

1. Koulaouzidis A, Plevris JN. Colon capsule endoscopy for detection of polyps and cancers: a step closer to non-invasive colon screening? J R Coll Physicians Edinb 2011;41:124–125.	Not fitting the inclusion criteria
2. Adler SN, Hassan C, Metzger Y, et al. Second-generation colon capsule endoscopy is feasible in the out-of-clinic setting. Surg Endosc 2014;28:570–575.	Not fitting the inclusion criteria
3. Adrián-de-Ganzo Z, Alarcón-Fernández O, Ramos L, et al. Uptake of colon capsule endoscopy vs colonoscopy for screening relatives of patients with colorectal cancer. Clin Gastroenterol Hepatol 2015;13:2293–2301.	Not fitting the inclusion criteria
4. Romero C, Rodriguez de Miguel C, Serradesanferm A, et al. Pillcam colon capsule for colorectal cancer screening: a prospective and comparative study with colonoscopy. Gastroenterology 2015;148:S759.	Included
5. Spada C, Riccioni ME, Hassan C, et al. PillCam colon capsule endoscopy: a prospective, randomized trial comparing two regimens of preparation. J Clin Gastroenterol 2011;45:119–124.	Included
6. Spada C, Hassan C, Cesaro P, et al. Prospective trial of PillCam colon capsule (CCE) vs CT-colonography (CTC) in the evaluation of patients with incomplete conventional colonoscopy (CC): an interim analysis. Gastrointest Endosc 2013;77:AB163.	Not fitting the inclusion criteria and duplication
7. Spada C, Hassan C, Ingrosso M, et al. A new regimen of bowel preparation for PillCam colon capsule endoscopy: a pilot study. Dig Liver Dis 2011;43:300–304.	Included
8. Spada C, Hassan C, Munos-Navaz MA, et al. Second-generation Pillcam colon capsule compared with colonoscopy. Dig Liver Dis 2011;43:S115.	Duplication
9. Spada C, Hassan C, Munoz-Navas MA, et al. Second-generation Pillcam colon capsule compared with colonoscopy. Gastrointest Endosc 2011;73:AB141.	Duplication
10. Spada C, Hassan C, Adler SN, et al. Flat colorectal lesions at PillCam colon capsule endoscopy (CCE). Gastrointest Endosc 2013;77:AB175.	Not fitting the inclusion criteria and duplication
11. Spada C, Hassan C, Marmo R, et al. Accuracy of colon capsule endoscopy as compared to colonoscopy in the detection of colorectal polyps: systematic review and meta-analysis. Dig Liver Dis 2010;42:S65–S66.	Not fitting the inclusion criteria
12. Postgate AJ, Fraser C, Fitzpatrick A, et al. Pillcam colon capsule endoscopy compared to colonoscopy in detection of colon polyps and cancers: interim analysis of a prospective multicentre trial. Gut 2008;57:A47.	Duplication
13. Alvarez Urturi C, Dedeu JM, Bessa X, et al. Colon capsule endoscopy compared to colonoscopy for familial screening of colorectal cancer. Gastrointest Endosc 2011;73:AB300.	Not fitting the inclusion criteria
14. Health Quality Ontario. Colon capsule endoscopy for the detection of colorectal polyps: an evidence-based analysis. Ont Health Technol Assess Ser 2015;15:1–39.	Not fitting the inclusion criteria
15. Rondonotti E, Mandelli G, Borghi C, et al. PillCam Colon Capsule 2® in the setting of colorectal cancer screening program: preliminary results of the comparison with a new integrated reference standard. Gastrointest Endosc 2013;77:AB466.	Duplication
16. Rondonotti E, Borghi C, Mandelli G, et al. Accuracy of capsule colonoscopy and computed tomographic colonography in individuals with positive results from the fecal occult blood test. Clin Gastroenterol Hepatol 2014;12:1303–1310.	Included
17. Rondonotti E, Mandelli G, Borghi C, et al. Pillcam Colon Capsule 2 in the setting of colorectal cancer screening program: preliminary results of the comparison with a new integrated reference standard. Dig Liver Dis 2013;45:S136.	Duplication
18. Eliakim R, Fireman Z, Gralnek IM, et al. Evaluation of the Pillcam Colon Capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy 2006;38:963–970.	Included
19. Eliakim R, Yassin K, Niv Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy 2009;41:1026–1031.	Included
20. Costamagna G, Spada C, Riccioni ME, et al. Evaluation of bowel preparation and procedure for Pillcam-Colon Capsule: an interim analysis. Gastrointest Endosc 2009;69:AB375.	Duplication
21. Giday S, Pickett-Blakely O, Mullin GE. Colon cancer diagnosed by capsule endoscopy. Clin Gastroenterol Hepatol 2008;6:A34.	Not fitting the inclusion criteria
22. Takamaru H, Kakugawa Y, Mori G, et al. Evaluation of the ability to visualize colorectal polyps with colon capsule endoscopy. Gastrointest. Endosc 2015;81:AB381.	Not fitting the inclusion criteria
23. Hagel AF, Gabele E, Raithel M, et al. Colon capsule endoscopy: detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies. Can J Gastroenterol Hepatol 2014;28:77–82.	Not fitting the inclusion criteria
24. Herrerías-Gutiérrez JM, Argüelles-Arias F, Caunedo-Álvarez A, et al. PillCamColon Capsule for the study of colonic pathology in clinical practice: study of agreement with colonoscopy. Rev Esp Enferm Dig 2011;103:69–75.	Not fitting the inclusion criteria
25. Holleran G, Leen R, O'Morain C, et al. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy 2014;46:473–478.	Included
26. Clara Luz MG, Sanchez Chavez X, Mejia Cuan LA, et al. Colon capsule endoscopy compared to conventional colonoscopy in Mexican population. Gastrointest Endosc 2012;75:AB349–AB350.	Not fitting the inclusion criteria

Supplementary Table 1. Continued

27. Baltes P, Bota M, Albert JG, et al. PillCam Colon2 after incomplete colonoscopy: a prospective multi-center study. Gastrointest Endosc 2014;79:AB584.	Not fitting the inclusion criteria
28. Pilz JB, Portmann S, Peter S, et al. Colon capsule endoscopy compared to conventional colonoscopy under routine screening conditions. BMC Gastroenterol 2010;10:66.	Included
29. Eliakim R. The PillCam Colon Capsule for colon cancer screening: comparison between the first- and second-generation capsules. Hospital Practice 2010;38:110–116.	Not fitting the inclusion criteria
30. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. Gastroenterology 2015;148:948–957.	Included
31. Oka S, Tanaka S, Saito Y, et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesion of the colon: prospective multicenter study in Japan. Gastrointest Endosc 2004;79:AB170–AB171.	Duplication
32. Suchanek S, Voska M, Majek O, et al. The efficiency of colonic capsule endoscopy in detection of colorectal polyps and cancers comparing to colonoscopy: multicenter, prospective cross over study. Gastrointest Endosc 2013;77:AB433–AB434.	Duplication
33. Suchanek S, Majek O, Tacheci I, et al. The efficiency of colonic capsule endoscopy in detection of colorectal polyps and cancers comparing to colonoscopy: multicenter, prospective cross over study. Gastrointest Endosc 2014;79:AB171.	Duplication
34. Suchanek S, Grega T, Voska M, et al. The efficiency of colonic capsule endoscopy in detection of colorectal polyps and cancers compared to colonoscopy: final results of multicenter, prospective, cross-over study. Gastrointest Endosc 2015;81:AB265.	Included
35. Adler SN, Sompolinsky Y, Metzger YC, et al. Capsule colonoscopy with Pillcam Colon 2 is feasible as an out-of-clinic procedure. Gastroenterology 2012;142:S53–S54.	Not fitting the inclusion criteria and duplication
36. Sacher-Huvelin S, Coron E, Gaudric M, et al. Colon capsule endoscopy vs colonoscopy in patients at average or increased risk of colorectal cancer. Aliment Pharmacol Ther 2010;32:1145–1153.	Included
37. Saito Y, Saito S, Oka S, et al. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointest Endosc 2015;82:861–869.	Not fitting the inclusion criteria
38. Schmidt C. Capsule endoscopy to screen for colon cancer scores low on sensitivity, high on controversy. J Natl Cancer Inst 2009;101:1444–1445.	Not fitting the inclusion criteria
39. Schoofs N, Deviere J, Van Gossum A. Pillcam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study. Endoscopy 2006;38:971–977.	Included
40. Sieg A. Capsule endoscopy compared with conventional colonoscopy for detection of colorectal neoplasms. World J Gastrointest Endosc 2011;3:81–85.	Not fitting the inclusion criteria
41. Sieg A, Friedrich K, Sieg U. Is Pillcam colon capsule endoscopy ready for colorectal cancer screening? a prospective feasibility study in a community gastroenterology practice. Am J Gastroenterol 2009;104:848–854.	Not fitting the inclusion criteria
42. Spada C, Hassan C, Barbaro B, et al. Colon capsule versus Ct colonography in patients with incomplete colonoscopy: a prospective, comparative trial. Gut 2015;64:272–281.	Not fitting the inclusion criteria
43. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc 2011;74:581–589.	Included
44. Triantafyllou K, Viazis N, Tsibouris P, et al. Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further workup in clinical practice. Gastrointest Endosc 2014;79:307–316.	Not fitting the inclusion criteria
45. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009;361:264–270	Included
46. De Ganzo ZA, Alarcon O, Gimeno-Garcia AZ, et al. Colon capsule endoscopy versus colonoscopy in familial colorectal cancer screening: a randomized controlled trial. Gastroenterology 2014;146:S-408.	Not fitting the inclusion criteria
47. Gay G, Delvaux M, Frederic M, et al. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy? results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. Am J Gastroenterol 2010;105:1076–1086.	Not fitting the inclusion criteria

Supplementary Table 2. Contacts With Authors for Additional Information

Author	Type of publication	Country(ies)	No. of centers	Study design
Romero,[27] Gastroenterology 2015 (abstract)	Abstract	Spain	1	Prospective, multicenter
Holleran,[28] Endoscopy 2014	Full article	Ireland	1	Prospective, single center

Supplementary Table 3. Main Characteristics of the Included Series

Author	Type of publication	Country(ies)	No. of centers	Study design
Eliakim,[4] Endoscopy 2006	Full article	Israel	3	Prospective, multicenter
Schoofs,[30] Endoscopy 2006	Full article	Belgium	1	Prospective, single center
Van Gossum,[3] N Engl J Med 2009	Full article	Belgium, Spain, France, Italy, United Kingdom, Germany	8	Prospective, multicenter
Sacher-Huvelin,[17] Aliment Pharmacol Ther 2010	Full article	France	16	Prospective, multicenter
Pilz,[31] BMC Gastroenterol 2010	Full article	Switzerland	1	Prospective, single center
Spada,[32] Dig Liver Dis 2011	Full article	Italy	3	Prospective, multicenter
Spada,[33] J Clin Gastroenterol 2011	Full article	Italy	1	Prospective, single center
Eliakim,[6] Endoscopy 2009	Full article	Israel	5	Prospective, multicenter
Spada,[5] Gastrointest Endosc 2011	Full article	Europe	8	Prospective, multicenter
Holleran,[29] Endoscopy 2014	Full article	Ireland	1	Prospective, single center
Rex,[8] Gastroenterology 2015	Full article	USA (10), Israel (6)	16	Prospective, multicenter
Suchanek,[16] Gastrointest Endosc 2015 (abstract)	Abstract	Czech Republic	5	Prospective, multicenter
Rondonotti,[34] Clin Gastroenterol Hepatol 2014	Full article	Italy	1	Prospective, single center
Romero,[28] Gastroenterology 2015 (abstract)	Abstract	Spain	1	Prospective, single center

Supplementary Table 4. Patients and Indications

	Patients			Indications (N)					
Author	No. enrolled	No. included	Mean age (*y*)	CRC screening	Family/personal history	Symptoms	FOBT +	Imaging tests +	Other
Eliakim,[4] Endoscopy 2006	91	84	57	39	0	20	0	24	8
Schoofs,[30] Endoscopy 2006	41	36	56	17	0	24	0	0	0
Van Gossum,[3] N Engl J Med 2009	332	320	58.5	0	0	208	0	112	0
Sacher-Huvelin,[17] Aliment Pharmacol Ther 2010	545	545	60	0	545	0	0	0	0
Pilz,[31] BMC Gastroenterol 2010	59	56	60	23	4	26	0	0	3
Spada,[32] Dig Liver Dis 2011	60	47	54	0	2	46	5	0	5
Spada,[33] J Clin Gastroenterol 2011	40	40	58.8	17	1	38	1	0	8
Eliakim,[6] Endoscopy 2009	104	98	48.8	31	33	20	21	0	0
Spada,[5] Gastrointest Endosc 2011	117	109	60	25	51	38	7	0	0
Holleran,[29] Endoscopy 2014	62	62	62.5	0	0	0	62	0	0
Rex,[8] Gastroenterology 2015	884	695	57	884	0	0	0	0	0
Suchanek,[16] Gastrointest Endosc 2015 (abstract)	225	225	59	225	0	0	0	0	0
Rondonotti,[34] Clin Gastroenterol Hepatol 2014	54	50	59.2	0	0	0	50	0	0
Romero,[28] Gastroenterology 2015 (abstract)	67	53	61.3	0	0	0	53	0	0

Supplementary Table 5. Regimens of Preparation, Capsule Cleansing Level, and Excretions

Author	C1/C2	PEG	Volume, *L*	Booster	Volume	Adequate cleansing level (%)	Excretion rate < 8 h (%)	Excretion rate 8–10 h (%)	Excretion rate > 10 h (%)
Eliakim,[4] Endoscopy 2006	C1	Yes	2 + 2	NaP	30 mL + 15 mL	84.4	NA	70	NA
Schoofs,[30] Endoscopy 2006	C1	Yes	3 + 1	NaP	45 mL + 30 mL	88	NA	84	NA
Van Gossum,[3] N Engl J Med 2009	C1	Yes	3 + 1	NaP	45 mL + 30 mL	72	69.1	92.8	99.7
Sacher-Huvelin,[17] Aliment Pharmacol Ther 2010	C1	Yes	3 + 1	NaP	45 mL + 30 mL	52	NA	91	NA
Pilz,[31] BMC Gastroenterol 2010	C1	Yes	2 + 2	NaP	45 mL + 30 mL	81	NA	NA	64
Spada,[32] Dig Liver Dis 2011	C1	Yes	3 + 1 2 + 2	NaP	45 + 30 30 mL + 15 mL	78	NA	83	NA
Spada,[33] J Clin Gastroenterol 2011	C1	Yes	3 + 1	NaP PEG	45 mL +30 mL (NaP) 0.5 L + 0.5 L(PEG)	35/53 (overall 42.5)	NA	100/75	NA
Eliakim,[6] Endoscopy 2009	C2	Yes	2 + 2	NaP	30 mL + 15 mL	78	81	NA	NA
Spada,[5] Gastrointest Endosc 2011	C2	Yes	2 + 2	NaP	30 mL + 25 mL	81	85	88	NA
Holleran,[29] Endoscopy 2014	C2	Yes	2 + 2	NaP SPS	45 mL + 30 mL (NaP) 45 mL + 30 mL (SPS)	92	73	NA	NA
Rex,[8] Gastroenterology 2015	C2	Yes	2 + 2	Suprep	6 oz + 3 oz	80	88	91	NA
Suchanek,[16] Gastrointest Endosc 2015 (abstract)	C2	NA	NA	NA	NA	90	NA	NA	NA
Rondonotti,[34] Clin Gastroenterol Hepatol 2014	C2	Macrogol 3350	1 + 1	NaP	30 mL + 15 mL	70	NA	NA	100
Romero,[28] Gastroenterology 2015 (abstract)	C2	Moviprep	1 + 1	Moviprep/ Gastrografin	0.5 L + 0.5 L/ 50 + 25 mL	79	75.5	NA	5.7

NA, not available; NaP, sodium phosphate; SPS, sodium picosulfate.

Supplementary Table 6. Quality Assessment of Included Studies Using the 14 Items of QUADAS Tool

QUADAS item	Eliakim[4]	Schoofs[30]	Van Gossum[3]	Sacher-Huvelin[17]	Pilz[31]	Spada[32]	Spada[33]	Romero[28]	Eliakim[6]	Spada[5]	Holleran[29]	Rex[8]	Suchanek[16]	Rondonotti[34]
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	No	No	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the whole sample or a random selection of the sample receive verification by using a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the reference standard independent of the index test, ie, the index test did not form part of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were uninterpretable/intermediate test results reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
14. Were withdrawals from the study explained?	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes

Supplementary Table 7. CCE Accuracy

Author	C1/C2	Polyps any size, %				Polyps ≥6 mm, %				Polyps ≥10 mm, %				CRC, %			
		Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Eliakim,[4] Endoscopy 2006	C1	69	81	74	78	63	94	67	91	—	—	—	—	—	—	—	—
Schoofs,[30] Endoscopy 2006	C1	76	64	83	54	60	73	46	83	—	—	—	—	—	—	—	—
Van Gossum,[3] N Engl J Med 2009	C1	72	78	—	—	64	84	—	—	60	98	—	—	74	74	—	—
Sacher-Huvelin,[17] Aliment Pharmacol Ther 2010	C1	58	71	73	56	39	88	47	85	35	97	52	95	60	100	60	100
Pilz,[31] BMC Gastroenterol 2010	C1	79	54	63	71	50	76	20	93	—	—	—	—	—	—	—	—
Spada,[32] Dig Liver Dis 2011	C1	—	—	—	—	100	95	78	100	100	100	100	100	—	—	—	—
Spada,[33] J Clin Gastroenterol 2011	C1	—	—	—	—	63	87	77	78	—	—	—	—	—	—	—	—
Eliakim,[6] Endoscopy 2009	C2	—	—	—	—	89	76	—	—	88	89	—	—	—	—	—	—
Spada,[5] Gastrointest Endosc 2011	C2	—	—	—	—	84	64	—	—	88	95	—	—	100	—	—	—
Holleran,[29] Endoscopy 2014	C2	95	65	79	90	—	—	—	—	89	96	89	96	100	—	—	—
Rex,[8] Gastroenterology 2015	C2	—	—	—	—	87	94	—	—	85	97	—	—	100	—	—	—
Suchanek,[16] Gastrointest Endosc 2015 (abstract)	C2	—	—	—	—	79	97	—	—	88	99	—	—	100	—	—	—
Rondonotti,[34] Clin Gastroenterol Hepatol 2014	C2	—	—	—	—	88.2	87.8	—	—	92.8	91.6	—	—	—	—	—	—
Romero,[28] Gastroenterology 2015 (abstract)	C2	100	100	—	94	87	88	—	—	88	94	—	—	—	—	—	—

NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.