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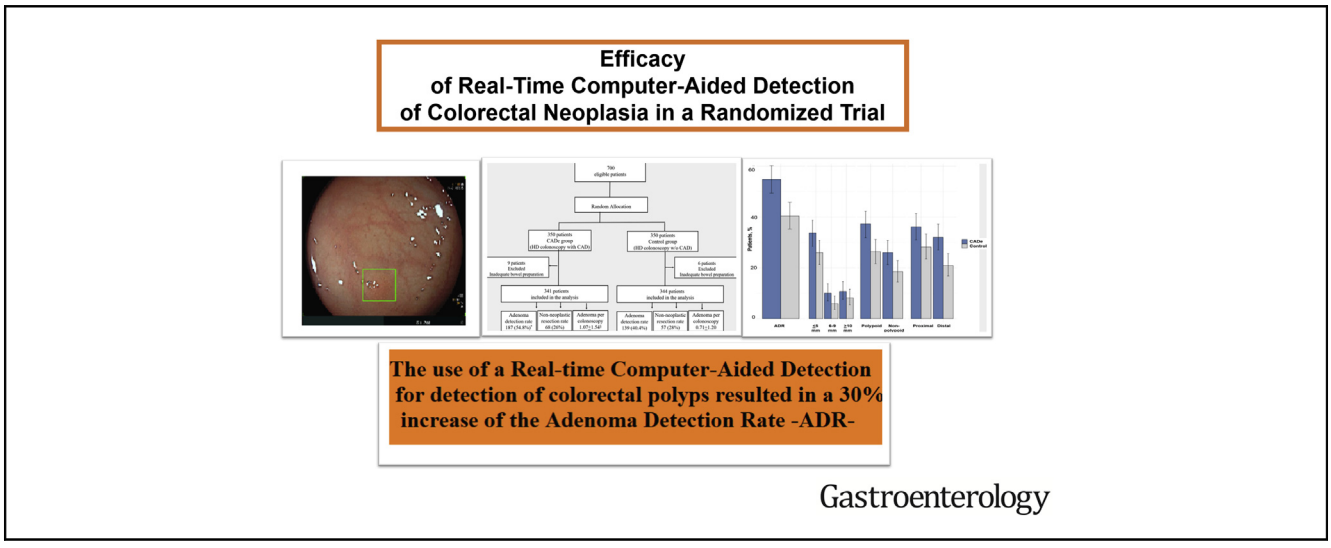
CLINICAL AT

Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial

Alessandro Repici,[1] Matteo Badalamenti,[1] Roberta Maselli,[1] Loredana Correale,[1] Franco Radaelli,[2] Emanuele Rondonotti,[2] Elisa Ferrara,[1] Marco Spadaccini,[1] Asma Alkandari,[3] Alessandro Fugazza,[1] Andrea Anderloni,[1] Piera Alessia Galtieri,[1] Gaia Pellegatta,[1] Silvia Carrara,[1] Milena Di Leo,[1] Vincenzo Craviotto,[1] Laura Lamonaca,[1] Roberto Lorenzetti,[4] Alida Andrealli,[2] Giulio Antonelli,[4] Michael Wallace,[5] Prateek Sharma,[6] Thomas Rosch,[7] and Cesare Hassan[4]

[1]Department of Gastroenterology, Humanitas Research Hospital, Milano, Italy; [2]Gastroenterology Department, Valduce Hospital, Como, Italy; [3]Thanyan Alghanim Center for Gastroenterology and Hepatology, Alamiri Hospital, Kuwait, Kuwait; [4]Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome, Italy; [5]Mayo Clinic, Jacksonville, Florida; [6]Kansas City Veterans Affairs Hospital, Kansas City, Missouri; and [7]Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg, Germany



BACKGROUND & AIMS: One-fourth of colorectal neoplasias are missed during screening colonoscopies; these can develop into colorectal cancer (CRC). Deep learning systems allow for real-time computer-aided detection (CADe) of polyps with high accuracy. We performed a multicenter, randomized trial to assess the safety and efficacy of a CADe system in detection of colorectal neoplasias during real-time colonoscopy. **METHODS:** We analyzed data from 685 subjects (61.32 ± 10.2 years old; 337 men) undergoing screening colonoscopies for CRC, post-polypectomy surveillance, or workup due to positive results from a fecal immunochemical test or signs or symptoms of CRC, at 3 centers in Italy from September through November 2019. Patients were randomly assigned (1:1) to groups who underwent high-definition colonoscopies with the CADe system or without (controls). The CADe system included an artificial intelligence–based medical device (GI-Genius, Medtronic) trained to process colonoscopy images and superimpose them, in real time, on the endoscopy display a green box over suspected lesions. A minimum withdrawal time of 6 minutes was required. Lesions were collected and histopathology findings were used as the reference standard. The primary outcome was adenoma detection rate (ADR, the percentage of patients with at least 1 histologically proven adenoma or carcinoma). Secondary outcomes were adenomas detected per colonoscopy, non-neoplastic resection rate, and withdrawal time. **RESULTS:** The ADR was significantly higher in the CADe group (54.8%) than in the control group (40.4%) (relative risk [RR], 1.30; 95% confidence interval [CI], 1.14–1.45). Adenomas detected per colonoscopy were significantly higher in the CADe group (mean, 1.07 ±1.54) than in the control group (mean 0.71 ± 1.20) (incidence rate ratio, 1.46; 95% CI, 1.15–1.86). Adenomas 5 mm or smaller were detected in a significantly higher proportion of subjects in the CADe group (33.7%) than in the control group (26.5%; RR, 1.26; 95% CI, 1.01–1.52), as were adenomas of 6 to 9 mm (detected in 10.6% of subjects in the CADe group vs 5.8% in the control group; RR, 1.78; 95% CI, 1.09–2.86), regardless of morphology or location. There was no significant difference between groups in withdrawal time (417 ± 101 seconds for the CADe group vs 435 ± 149 for controls; $P = .1$) or proportion of subjects with resection of non-

neoplastic lesions (26.0% in the CADe group vs 28.7% of controls; RR, 1.00; 95% CI, 0.90–1.12). **CONCLUSIONS:** In a multicenter, randomized trial, we found that including CADe in real-time colonoscopy significantly increases ADR and adenomas detected per colonoscopy without increasing withdrawal time. ClinicalTrials.gov no: 04079478

Keywords: Artificial Intelligence; Adenoma Per Colonoscopy; Comparison; Early Detection.

One-fourth of colorectal neoplasia is missed at screening colonoscopy,[1] representing the main cause of interval colorectal cancer (CRC),[2,3] and resulting in an unacceptable variability in the key quality indicator, namely adenoma detection rate (ADR), among endoscopists.[4,5]

Failure in polyp recognition is a major determinant for this miss rate of colorectal neoplasia.[6,7] Each colonoscopy is made of approximately 50,000 frames, corresponding to approximately 25 to 30 frames per second, and 1 polyp may be recognizable only in a few frames, explaining how failure in polyp recognition is likely to occur, irrespectively of the endoscopy setting.

The theoretical and technological advances in Deep Learning led to the development of computer-aided polyp detection (CADe) systems. These systems showed a high accuracy in polyp recognition when retrospectively applied to endoscopy videos or images both in terms of true- and false positive results.[8–11]

The impact of CADe on neoplasia detection may be considered as a good proxy for the efficacy of these systems in reducing the miss rate, as gradients in ADR and adenomas per colonoscopy (APC) are inversely related with the miss rate after normalizing for disease prevalence.[1] However, polyp detection does not only depend on polyp recognition, the main factor currently addressed by CADe, as it is also affected by the degree of exposure of the mucosa that in turn is related with the speed of withdrawal time, endoscopist skill, level of cleansing, and other factors.[4] Thus, the actual effect of CADe on detection of colorectal neoplasia is still unclear. The only available clinical study adopted an experimental setting with 2 monitors (one with and one without CADe) due to the unfeasibility of a simultaneous CADe diagnosis.[12] A new CADe system (GI-Genius; Medtronic, Minneapolis, MN) avoids the need of a second display to show the artificial intelligence detection box on the endoscopy image, and as such it is fully integrated in the endoscopy workflow, enabling real-time video processing at the same frame rate as the standard procedure, without requiring any artificial modifications of the usual colonoscopy technique.

In addition to its efficacy, it is relevant to qualify CADe safety indicators, to better understand how it is going to impact CRC prevention (eg, possible unnecessary resections, withdrawal time).

Aim of the AID (Artificial Intelligence for Colorectal Adenoma Detection) study was to assess the safety and efficacy of a CADe system for the detection of colorectal neoplasia.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Deep learning systems allow for real-time computer-aided detection (CADe) of polyps with high-accuracy, but these systems have not been tested in randomized trials.

NEW FINDINGS

In randomized trial, inclusion of CADe in colonoscopy significantly increased adenoma detection rates and adenomas detected per colonoscopy, without increasing withdrawal time. Higher proportions of adenomas smaller than 5 mm and 6–9 mm were detected with CADe, regardless of morphology or location.

LIMITATIONS

This study was performed in an expert setting; studies are needed for inexperienced endoscopists.

IMPACT

Including CADe in colonoscopy examinations increases detection of adenomas without affecting safety.

Methods

This parallel, randomized, multicenter trial was performed in 3 Italian endoscopy centers participating in the organized population CRC screening programme (institutional review board: ICH2363/2019). The study was reported according to the CONSORT guidelines for randomized controlled trials and was registered on the ClinicalTrial.gov (NCT: 04079478). This was a no-profit study, and no funding was received or solicited, except the loan of the equipment by Medtronic. All authors had access to the study data and reviewed and approved the final manuscript.

Study Population

The target population included 40- to 80-year-old subjects undergoing colonoscopy for primary CRC screening or post-polypectomy surveillance, as well as for workup following fecal immunohistochemical test (FIT) positivity (cutoff = 20 μg Hb/g feces) or for symptoms/signs. Patients were excluded in case of personal history of CRC, or inflammatory bowel disease, previous colonic resection, antithrombotic therapy precluding polyp resection, and lack of informed written consent.

Artificial Intelligence (CADe)

A Convolutional Neural Network (GI-Genius; Medtronic) was trained and validated (99.7% per-lesion sensitivity, 0.9% of false positive frames[10]) using a series of videos of 2684 histologically confirmed polyps from 840 patients enrolled in a high-quality randomized trial.[13] This CADe receives as input the digital image from the endoscopy processor and outputs the

List of abbreviations used in this paper: **ADR, adenoma detection rate; APC, adenomas per colonoscopy; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; CADe, computer-aided detection; RR, relative risk; SSL, sessile serrated lesion.**

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coordinates of a bounding box only when an instance of the target polyp is recognized in the image. The output appears on the same endoscopy screen as the system latency in outputting the video processor images with the detections is not perceivable by the user (1.52 ± 0.08 μs), thus allowing real-time assessment (Figure 1).

Randomization

Before colonoscopy initiation, eligible subjects were randomized in a 1:1 ratio by the endoscopists to receive colonoscopy with or without CADe in both insertion and withdrawal phases of the procedure. Randomization was based on a a list of random numbers generated for each center by the coordinating center. Randomization was stratified by gender, age, and personal history of adenomas. The operator was not blinded to the study arm assigned to the patient.

Colonoscopy Procedures

Colonoscopies were performed by 6 experienced endoscopists (2 for each center; >2000 screening colonoscopies) in 3 centers participating in the organized screening program. All procedures were performed with a high-definition ELUXEO 700 series (EC-760R, EC-760ZP, FUJIFILM Co., Tokyo, Japan) or EXERA III (Olympus CV-190; Olympus Co., Tokyo, Japan). For the purpose of the study, use of magnification, chromoendoscopy, or light-modification technologies was restricted only for polyp characterization at endoscopist's discretion. Bowel preparation was evaluated and graded by the endoscopist performing the examination, using the Boston Bowel Preparation scale.[14] Subjects with 0 or 1 in any 1 of the 3 segments were excluded from the primary analysis. The endoscopist and facility staff were allowed to adopt their standard procedures for subject management and monitoring, including use of conscious sedation. Caecal intubation was assessed by the endoscopist by the identification of the ileocecal valve and the appendix orifice via photo documentation.

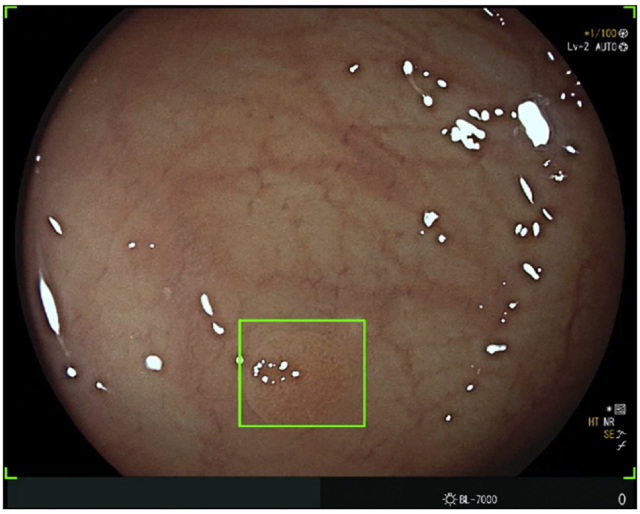

Figure 1. CADe is able to identify and localize the adenomatous lesion in real-time colonoscopy. The output appears on the same screen of the endoscopy system without affecting the routine technique of the operator.

Intubation time and inspection time during withdrawal were measured using a stopwatch, pausing during therapeutic interventions and washing. Endoscopists were required to comply with a minimum of 6 minutes of inspection (ie, clean withdrawal time).[15,16] All polyps were classified according to their location, size, and morphology according to Paris classification.[17] Location was considered proximal if proximal to the splenic flexure. All polyps were removed (biopsy for non-resectable lesions), irrespective of size, color, or subjective interpretation, with the exception of diminutive hyperplastic-appearing polyps located in the rectum and, according to the judgment of the endoscopists, not clinically significant.

Histopathology

All resected or biopsy specimens were fixed in 10% buffered formalin solution in separate jars. They were processed and stained for histopathology using standard methods and evaluated by expert pathologists participating in the organized screening program (one in each center), who were blinded to the assigned examination mode. All lesions were classified according to Vienna classification.[18] An advanced adenoma was defined as an adenoma ≥10 mm and/or with villous component ≥20%, and/or high-grade dysplasia.

Outcome Measures

The primary outcome was the ADR according to intervention arm. ADR was defined as the proportion of patients with at least 1 histologically proven adenoma or carcinoma.[13] Sessile serrated lesions (SSLs) were not computed in ADR calculation; Secondary outcomes were proximal ADR, total number of polyps detected, SSL detection rate, mean number of APCs, cecal intubation rate, and withdrawal time. The proximal ADR was defined as the prevalence of patients with at least 1 adenoma detected proximal to the splenic flexure (including cecum, ascending, and transverse colon). APC was defined as the total number of adenomas divided by the number of colonoscopies performed. APPC was defined as the total number of adenomas divided by the total of colonoscopies where at least 1 adenoma was discovered. We also defined non-neoplastic resection rate as the proportion of patients with no adenoma or SSL within any excised lesions who had undergone at least 1 excision with histopathological examination.[13]

Statistical Considerations

Sample size. The sample size was calculated based on the evaluation of primary outcome that is the per-patient ADR. A sample size of 322 patients per arm was required, based on the expected ADR of 35% for both arms, a noninferiority margin of 10%, power of 90%, and an alpha level of 2.5% (1-sided). Noninferiority was met for the primary endpoint if the lower 2-sided 95% confidence interval (CI) excluded a 10% or greater difference in favor of the control group. The 10% noninferiority margin reflects a typical maximum clinically acceptable difference for comparative studies of this type. If noninferiority was demonstrated for the primary endpoint, the endpoint was assessed for superiority (1-sided $P < .025$) using the Fisher exact test.

Statistical analysis. The primary outcome analysis was the comparison of ADR between the 2 study arms. Intention-to-treat (and per protocol) analysis was conducted. Differences

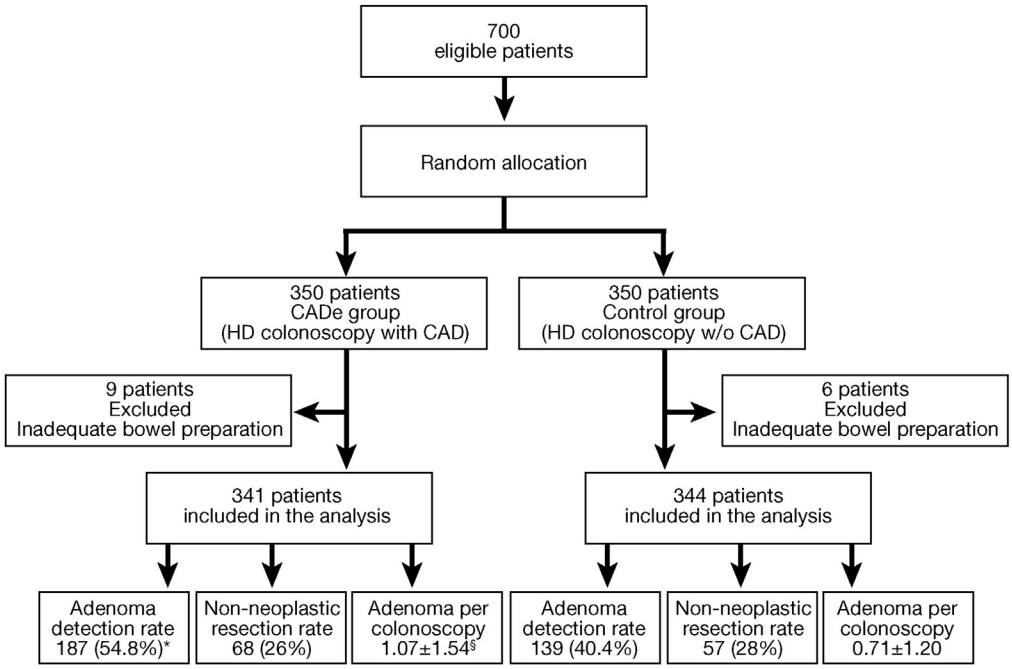

Figure 2. Study flow chart including clinical outcomes. *1.30 (95% CI, 1.14-1.45). §Incidence Rate Ratio 1.46 (95% CI, 1.15-1.86).

were expressed as relative risk (RR) with 95% CIs. Categorical variables were described by frequency counts and percentages. Quantitative variables were described by mean and standard deviations. Chi-square and *t*-tests were used to compare categorical and continuous variables between the 2 groups, respectively. Multivariate estimations of prevalence ratios were obtained using log-binomial regression; adjustments were made for age, gender, and colonoscopy indication. We also estimated the prevalence of adenomas by colonic location (distal, including the descending-sigmoid colon, and rectum) vs proximal colon (including cecum, ascending, and transverse colon), and by morphology (Paris classification: polypoid vs nonpolypoid lesions) in the 2 arms. The overall APC was calculated in addition to APC stratified by age, gender, and colonoscopy indication. Using Poisson regression, we calculated incident rate ratios to assess the relationship among study arm, age, gender, and colonoscopy indication. Last, a per-polyp analysis to assess differences in adenoma location, size, and morphology was also performed using mixed effects logistic regressions to control for multiple lesions per patient. Data were reported as odds ratios. Mixed effects models were fit with a random intercept and treatment as a fixed effect. We did not control for clustering within endoscopy center. A $P < .05$ was considered statistically significant. All statistical analyses were performed using R software version 3.5.1 (2018–07–02).

Results

Study Population

A total of 700 subjects were considered eligible for the study between September and November 2019. After the exclusion of 15 patients (Figure 2), the study cohort was represented by 685 (men: 49.2%, mean age 61.32 ± 10.2 years) randomized patients. Of these, 341 were allocated in the CADe arm, and 344 in the control; no difference in clinical indication between the 2 arms was found (Table 1), and it was overall primary CRC screening or post-polypectomy surveillance in 46.3% (317/685), workup of FIT+ in 30.2% (207/685), and gastrointestinal symptoms in 23.5% (161/685). No difference between CADe and control was observed in term of adequate (Boston Bowel Preparation Scale ≥2 in all colonic segments) cleansing (339/341, 99.4% vs 342/344, 99.4%; $P = 1.0$) and cecal intubation rate (326/341 subjects, 95.6% vs 339/344, 98.5%; $P = .7$).

Per-Patient Analysis

In the CADe group, 187 of 341 patients were diagnosed with at least 1 adenoma or CRC at colonoscopy as compared with 139 of 344 patients in the control group, corresponding to an ADR of 54.8% and 40.4%, respectively (Figure 3). After adjusting for age, gender, and indication, ADR was significantly higher in the CADe as compared with control group (RR, 1.30; 95% CI, 1.14–1.45; Table 2; Supplementary Table 1). The per protocol analysis produced similar results (Supplementary Table 2).

Regarding morphology (Table 2), the rate of patients with nonpolypoid lesions was higher in the CADe than in control group (90/338 [26.6%] vs 63/343 [18.4%]; RR, 1.42 [1.09–1.79]), as well as that with polypoid lesions (37.3% vs 26.5%; RR, 1.36 [1.12–1.62]). Regarding polyp size (Table 2), the proportion of patients with <10 mm adenomas was higher in the CADe group (151/341 [44.3%]) than in the control group (111/344, 32.3%; RR, 1.33 [1.13–1.53]), whereas no difference for those with ≥10 mm as largest lesion was observed. As shown in Table 2, the difference between the 2 arms was significant for both ≤5 mm (RR, 1.26; 95% CI, 1.01–1.52) and 6- to 9-mm adenomas (RR, 1.78 [1.09–2.86]). Regarding location (Table 2), the proportion of patients with proximal adenomas was higher

Table 1. Patients' Characteristics According to Intervention Arm

Variable	CADe (341 patients)	Control (344 patients)	*P*
Mean age (SD), y	61.5 (9.7)	61.1 (10.6)	.442
Gender, n (%)			.541
Female	169 (49.6)	179 (52.0)	
Male	172 (50.4)	165 (49.6)	
Indication for colonoscopy, n (%)			.818
FIT+	102 (29.9)	105 (30.5)	
Primary CRC screening	77 (22.6)	76 (22.1)	
Surveillance	86 (25.2)	78 (22.7)	
GI Symptoms	76 (22.3)	85 (24.7)	
Mean BBPS score (SD)			
Right colon	2.4 (0.50)	2.4 (0.52)	.748
Transverse	2.5 (0.50)	2.5 (0.52)	.943
Left colon	2.5 (0.51)	2.5 (0.50)	.645
Adequate preparation (BBPS ≥2 in all segments)	339 (99.4)	342 (99.4)	.999
Mean insertion time (IQR), min	9.0 (5–11)	8.1 (2–10)	.056
Mean inspection time (IQR), s[a]	7.3 (6–8)	7.0 (6–8)	.100
No. of polyps of any histology per patient (range)	1.89 (0–13)	1.24 (0–9)	<.001

FIT, fecal immunochemical test; BBPS, Boston Bowel Preparation Scale; IQR, interquartile range; SD, standard deviation.
[a]The information was missing in 7 and 13 cases in CADe e Control arm, respectively.

in the CADe group (123/341 [36.1%]) than in the control group (97/344, 28.2%; RR, 1.28 [1.03–1.59]), as well as that with distal adenomas (149/341 [32.0%] vs 69/344 [20.1%], 37%; RR, 1.53 [1.18–1.98]). Regarding multiplicity, 131 (19.1%) patients had ≥2 adenomas: percentages of patients with multiple adenoma in CADe and control group were 23.2% (79) and 15.1% (52), respectively (RR, 1.50; 95% CI, 1.19–1.95).

Regarding histology, 45 patients were diagnosed with advanced neoplasia in the CADe group, compared with 36 control group patients, corresponding to a detection rate of advanced neoplasia of 13.2% and 8.2%, respectively (adjusted RR, 1.22; 95% CI, 0.80–1.93, Table 2; Supplementary Table 1). No difference in the proportion of patients with at least 1 SSL was found between the 2 groups (CADe, 7.0% vs control, 5.2%; $P = .326$).

Individual detection rates at per-center and endoscopist levels are provided in Supplementary Figures 1 and 2), as well as ADR according to indications.

Non-neoplastic Resection Rate

Overall, 460 (67.1%) of 685 patients had polyp resections. Of these, 125 (27.1%) of 460 did not have histologically proven adenomas, SSLs, or CRCs. The non-neoplastic resection rates were 68 (26.0%) of 262 and 57 (28.8%) of 198 in the CADe and control group, respectively (RR, 1.00; 95% CI, 0.90–1.12; $P = .940$).

Per-Polyp Analysis

In the 262 and 198 patients with polyp resection in the CADe and control groups, 353 and 243 adenomatous polyps were detected, respectively. Characteristics of detected polyps and cancers according to intervention arm are summarized in Supplementary Tables 3 and 4.

The APC overall was 0.87 ± 1.39 (Table 3), and it was significantly higher in the CADe than in the control group (1.07 ± 1.54 vs 0.71 ± 1.20; incident rate ratio, 1.46; 95% CI, 1.15–1.86). The association between the APC and study arm remained significant after adjusting for gender, indication, and withdrawal time in a random effect model (odds ratio, 1.80; 95% CI, 1.14–2.81) (Supplementary Table 5).

Differences in APC between CADe and control group were also analysed according to polyp characteristics, as detailed in (Table 3). A statistically significant increase in APC between CADe and control group was found for both polypoid and nonpolypoid lesions, as well as for both proximal and distal locations. Regarding polyp size the difference was significant only for <10 mm polyps.

Discussion

The addition of real-time CADe to colonoscopy resulted in a 30% and 46% relative increase in ADR and APC, demonstrating its efficacy in improving the detection of colorectal neoplasia at screening and diagnostic colonoscopy. Safety of CADe was demonstrated by the lack of increase of both useless resections and withdrawal time, as well as by the exclusion of any underskilling in the study period. CADe efficacy appeared to be independent of morphology and location of neoplasia, and it was mainly explained by the additional detection of ≤5 mm and 6- to 9-mm polyps.

CADe was already shown to be highly accurate for polyp recognition in retrospective assessment of videos with already diagnosed polyps[8–10]; however, there was uncertainty on its impact on polyp detection that also depends on the degree of mucosa exposure. The 14% absolute increase in ADR obtained by CADe in our study indicates that failure in polyp recognition is a clinically relevant cause of miss rate. Of note, the efficacy of CADe in reversing such miss

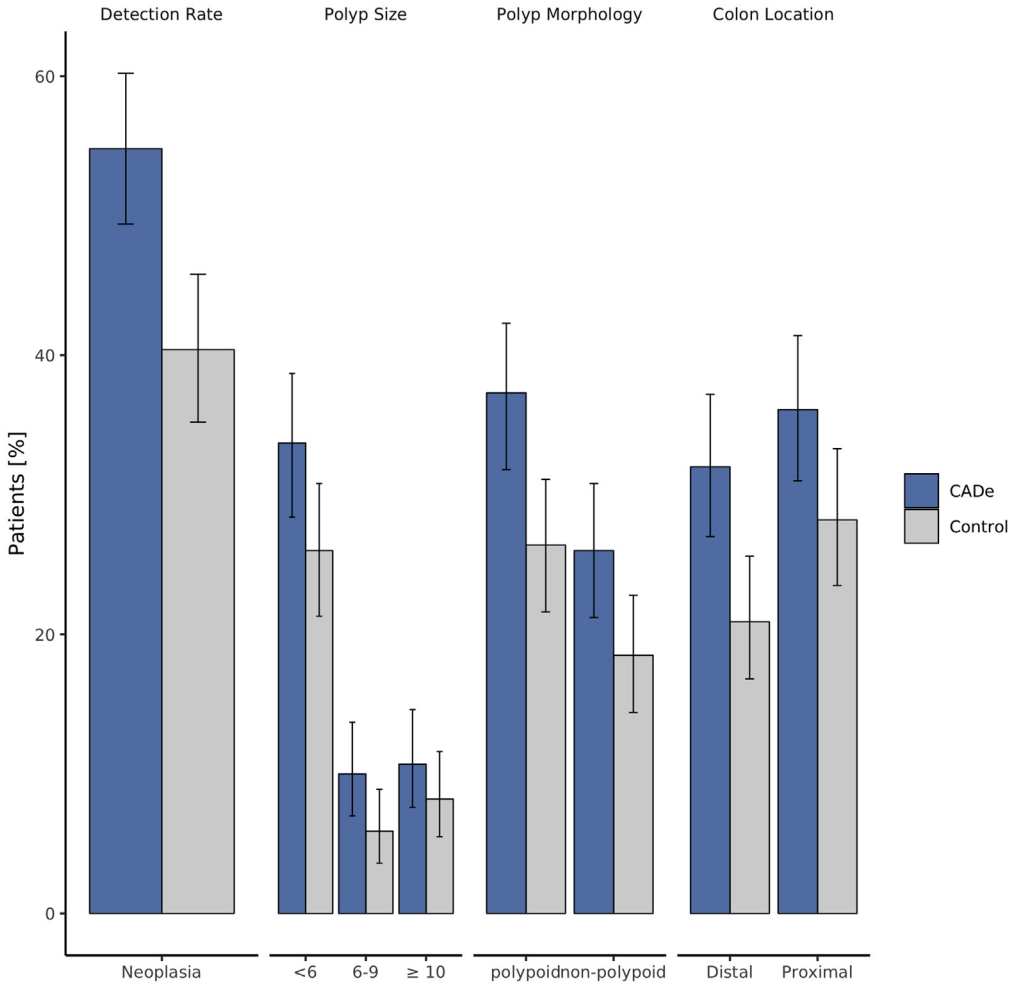

Figure 3. (Per-patient) Adenoma detection rate as well as (Per-patient) ADR by adenomas features. (*A*) Adenoma Size Category, large (≥10 mm) vs small (<10 mm). (*B*) Adenoma Morphology, polypoid: (pedunculated [0–1 p], sessile [0–1 s] or mixed [0–1 sp]) vs non-polypoid lesions: (superficial slightly elevated [IIa], flat [IIb], superficial depressed [IIc], and excavated [III] types). (*C*) SSLs. (*D*) Colon location, proximal colon (cecum, ascending, and transverse) vs distal colon (descending, sigmoid, and rectum). The *asterisk* indicates statistically significant difference between the 2 arms.

rate also indicates that the same operator who missed the lesion in the first place was able to correctly diagnose it when the lesion was presented by the CADe. This underlines that the main cognitive challenge in polyp recognition is the discrimination between the candidate lesion and the surrounding healthy mucosa, whereas its correct characterization as neoplastic tissue, that occurs after CADe detection, is apparently a much easier task. This is well in line with previous evidence that the use of dye-spray or electronic chromoendoscopy was able to increase the ADR of the operator by emphasizing the contrast between the neoplastic and healthy tissue.[13,19] The additional advantage of CADe is that it completely automatizes, by presenting a well-delimited box around the putative lesion (Figure 1), the detection phase, whereas chromoendoscopy still requires the endoscopist to identify the lesion in the first place. Future studies should address whether the addition of CADe over chromoendoscopy further improves neoplasia detection over CADe alone.

Our study setting allowed us to assess the safety of CADe colonoscopy for experienced endoscopists. Differently from previous studies based on experimental setting,[12] we fully integrated CADe in the endoscopy system, completely mimicking the usual routine of the operators by overimposing the CADe box over the same endoscopic screen. Our study excludes any underskilling effect (ie, an ADR reduction) on the operators, marginalizing any possibility for the CADe to distract or reduce the level of alertness of the operator. Second, we excluded any clinically relevant effect of non-neoplastic resections due to CADe. First, the actual number of patients with useless resection of non-neoplastic polyps did not increase. Second, there was no increase in the withdrawal time. Both of these outcomes indicate that the endoscopist is fast and accurate in lesion characterization, discarding non-neoplastic lesions detected by CADe with the same competence as when detected without it. Although we did not assess the actual number of false positive activations by the system, as this would have altered the routine setting of our study, we already showed such number to be less than 1% of the whole colonoscopy video.[10]

The contribution of small lesions to the gradient between the 2 study arms is in line with pooling of tandem studies showing such lesions to be associated with miss rate at colonoscopy.[20] When considering the additional detection as a proxy for a reduction of miss rate, CADe was able to increase the ADR by targeting the miss rate of the most subtle lesions in the colonoscopy field. The correspondence

Table 2. Detection Rate According to Intervention Arm, As Well As Per Patient Distribution of Adenomatous Polyps According to Morphology, Size, and Location

Per-patient analysis[a]	CADe (n = 341)	Control (n = 344)	Total Number (N=685)	RR [95% CI]	*P*
Histology					
All adenomas and CRCs	187 (54.8)	139 (40.4)	326 (47.6)	1.30 (1.14–1.45)[b]	<.001
Non-advanced adenomas	142 (41.6)	103 (29.9)	245 (35.8)	1.35 (1.13–1.57)	.001
Advanced adenomas[c]	35 (10.3)	33 (7.3)	68 (9.9)	1.07 (0.68–1.66)	.769
Adenocarcinoma (CRC)	10 (2.9)	3 (0.9)	13 (1.9)	3.36 (0.93–12.11)	.067
Sessile serrated Lesion	24 (7.0) [d]	18 (5.2)	42 (6.1) [d]	1.34 (0.75–2.37)	.326
Non-neoplastic polyp[e]	68 (19.9)	57 (16.6)	125 (18.2)	1.20 (0.88–1.65)	.254
Size category[f]					
5 mm	115 (33.7)	91 (26.5)	206 (30.1)	1.26 (1.01–1.52)	.038
6–9 mm	36 (10.6)	20 (5.8)	56 (8.2)	1.78 (1.09–2.86)	.025
≥10 mm	36 (10.6)	28 (9.1)	64 (9.3)	1.29 (0.81–2.02)	.278
Morphology[g]					
Polypoid[h]	126 (37.3)	90 (26.2)	216 (35.1)	1.36 (1.12–1.62)	.003
Nonpolypoid[i,j]	90 (26.6)	63 (18.4)	153 (22.5)	1.42 (1.09–1.79)	.010
Location[f]					
Proximal colon[k,l]	123 (36.1)	97 (28.2)	220 (32.1)	1.28 (1.03–1.59)	.028
Distal colon[m]	109 (32.0)	69 (20.1)	181 (26.4)	1.53 (1.18–1.98)	.001

[a]It refers to proportion of patients with at least 1 adenoma or CRC, unless otherwise specified.
[b]After adjustment for age, gender, and colonoscopy indication; crude RR for adenoma detection rate: 1.36 (1.16–1.59); crude RR for advanced neoplasia detection rate: 1.30 (0.86–1.99).
[c]Advanced adenoma was defined as an adenoma of 10 mm or larger, or as an adenoma (irrespective of size) with at least 20% villous histology or with high-grade dysplasia.
[d]Two SSL with cytological dysplasia, corresponding to a cumulative SSL with dysplasia/all SSL ratio of 4.8%.
[e]Normal, hyperplastic, inflammatory and others.
[f]According to the size of the largest neoplastic lesion.
[g]There were 4 cases with missing data: 3 in the CADe and 1 in the control group.
[h]Elevated more than 2.5 mm above the mucosal layer: pedunculated (0–1 p), sessile (0–1 s) or mixed (0–1 sp).
[i]Nonpolypoid lesions: superficial slightly elevated (IIa), flat (IIb), superficial depressed (IIc), and excavated (III) types.
[j]Including 29 (8.6%) CADe and 14 (4.1%) control group cases who had synchronous polypoid adenomas.
[k]Cecum, ascending, and transverse.
[l]Including 45 (13.2%) CAD-e and 27 (7.8%) control cases who had synchronous adenomas in the distal colon.
[m]Descending, sigmoid, and rectum.

between the increase in ADR and APC underlines the efficacy of CADe not only in classifying qualitatively a patient as an adenoma-bearing or negative one, but also in correctly diagnosing all the burden of neoplasia that occur in each single patient. Such synergic effect should anticipate a more profound result in terms of post-colonoscopy CRC prevention. Of note, the proportion of patients with multiplicity was higher in the CADe as compared with the control arm.

The independence of the CADe effect from location and morphology is also in line with previous tandem studies that excluded a role for proximal location as well as for sessile versus flat morphology in the miss rate of neoplasia at colonoscopy.[20] Contrarily, the association between increased yield and ≤10-mm size was not unexpected as miss rate for these lesions appeared to be substantially superior to those for ≥10-mm lesions in the pooling of tandem studies.[20] Due to the high prevalence and subtle appearance, diminutive and small lesions may be considered as a proxy for the technical competence of the endoscopist. Such competence in turn has been strictly associated with the degree of post-colonoscopy CRC risk.

There are limitations to our analysis. First, we could not exclude a psychological bias, as the operator was aware of the randomized intervention. However, the ADR in the control arm was actually superior (40% vs 35%, Supplementary Table 6) to what it was previously recorded in the clinical setting of 1 of the 3 centers and used to estimate the sample size. The ADR in the control arm was approximately 2-fold superior to the previous CADe study with an experimental setting,[12] being more representative of the Western-like endoscopy setting. In addition, the equivalence in withdrawal time exclude a somewhat reduced degree of mucosal exposure in the control arm. When selecting only the FIT+ patients, the ADR in the control arm was also in line with previous studies from our group (Supplementary Table 6). Finally, the increase in ADR was consistent in all the 3 centers involved (Supplementary Table 6), marginalizing the possibility of operator-related bias. Third, we did not include low-detectors, inexperienced, or non-gastroenterologist endoscopists in our study. Thus, there is uncertainty on whether CADe would be equally beneficial in these categories for the following reasons. First, low-detectors have been shown to be suboptimal in the technical exposure of colorectal mucosa. Thus, the additional contribution of an improved polyp recognition with CADe is uncertain. Second, we cannot exclude that less

Table 3. Per Polyp Analysis: Mean Number of APCs and Poisson Regression Analysis by Polyp Characteristics Among Study Participants (n = 685)

	CAD-e	Control	
Per polyp analysis	APC (SD)	APC (SD)	IRR[95% CI]
Morphology[a]			
Polypoid[b]	0.61 (1.20)	0.42 (0.92)	1.44 (1.05–1.96)
Nonpolypoid[c,d]	0.42 (0.94)	0.28 (0.83)	1.47 (1.00–2.15)
Size[a]			
<10 mm	0.92 (1.40)	0.62 (1.08)	1.50 (1.17–1.91)
≥10 mm	0.11 (0.35)	0.09 (0.31)	1.07 (0.66–1.74)
Location[a]			
Proximal colon[e,f]	0.60 (1.10)	0.45 (0.92)	1.35 (1.00–1.81)
Distal colon[g]	0.43 (0.79)	0.26 (0.80	1.60 (1.14–2.07)

IRR, incidence risk ratio as adjusted for patient age, gender, and indication.
[a]There were missing data in 3 CADe cases and 3 control case.
[b]Elevated more than 2.5 mm above the mucosal layer: pedunculated (0–1 p), sessile (0–1 s) or mixed (0–1 sp).
[c]Nonpolypoid lesions: superficial slightly elevated (IIa), flat (IIb), superficial depressed (IIc), and excavated (III) types.
[d]Including 29 (8.5%) CADe and 14 (4.1%) control group cases who had synchronous polypoid adenomas.
[e]Including 45 (13.2%) CAD-e and 30 (8.7%) control cases who had synchronous adenomas in the distal colon.
[f]Cecum, ascending, and transverse.
[g]Descending, sigmoid, and rectum.

experienced endoscopists would remove an excess of non-neoplastic lesions triggered by false positive results, differently from what reported in our analysis. Alternatively, endoscopists with less experience could require more time to assess the false positives by CADe, affecting the efficiency of the colonoscopy procedure (ie, prolonging the withdrawal time).

In conclusion, we showed the safety and efficacy of integrating CADe in real-time colonoscopy. The substantial improvement of ADR and APC without increasing the removal of non-neoplastic lesions is likely to improve the quality of colonoscopy without affecting its efficiency.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.04.062.

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Correspondence
Address correspondence to: Alessandro Repici, MD, Digestive Endoscopy Unit, IRCCS Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano Milano, Italy. e-mail: alessandro.repici@hunimed.eu.

CRediT Authorship Contributions
Alessandro Repici, MD (Conceptualization: Lead; Supervision: Equal; Writing – original draft: Lead). Matteo Badalamenti, MD (Conceptualization: Equal; Data curation: Lead; Writing – original draft: Equal). Roberta Maselli, MD, PhD (Supervision: Equal; Writing – review & editing: Equal). Loredana Correale, \ (Data curation: Equal; Formal analysis: Lead). Franco Radaelli, MD (Supervision: Equal; Writing – review & editing: Equal). Emanuele Rondonotti, MD (Supervision: Equal; Writing – review & editing: Equal). Elisa Ferrara, MD (Supervision: Equal; Writing – review & editing: Equal). Marco Spadaccini, MD (Conceptualization: Equal; Supervision: Equal; Writing – review & editing: Equal). Asma Alkandari, MD (Writing – review & editing: Equal). Alessandro Fugazza, MD (Supervision: Equal; Writing – review & editing: Equal). Andrea Anderloni, MD, PhD (Supervision: Equal; Writing – review & editing: Equal). Piera Alessia Galtieri, MD (Supervision: Equal; Writing – review & editing: Equal). Gaia Pellegatta, MD (Supervision: Equal; Writing – review & editing: Equal). Silvia Carrara, MD (Supervision: Equal; Writing – review & editing: Equal). Milena Di Leo, MD (Supervision: Equal; Writing – review & editing: Equal). Vincenzo Craviotto, MD (Supervision: Equal; Writing – review & editing: Equal). Laura Lamonaca, MD (Supervision: Equal; Writing – review & editing: Equal). Roberto Lorenzetti, MD (Supervision: Equal; Writing – review & editing: Equal). Andrealli Alida, MD (Supervision: Equal; Writing – review & editing: Equal). Giulio Antonelli, MD (Supervision: Equal; Writing – review & editing: Equal). Michael Wallace, MD (Supervision: Equal; Writing – review & editing: Equal). Prateek Sharma, MD (Supervision: Equal; Writing – review & editing: Equal). Thomas Rosch, MD (Supervision: Equal; Writing – review & editing: Equal). Cesare Hassan, MD, PhD (Data curation: Equal; Supervision: Equal; Writing – original draft: Lead).

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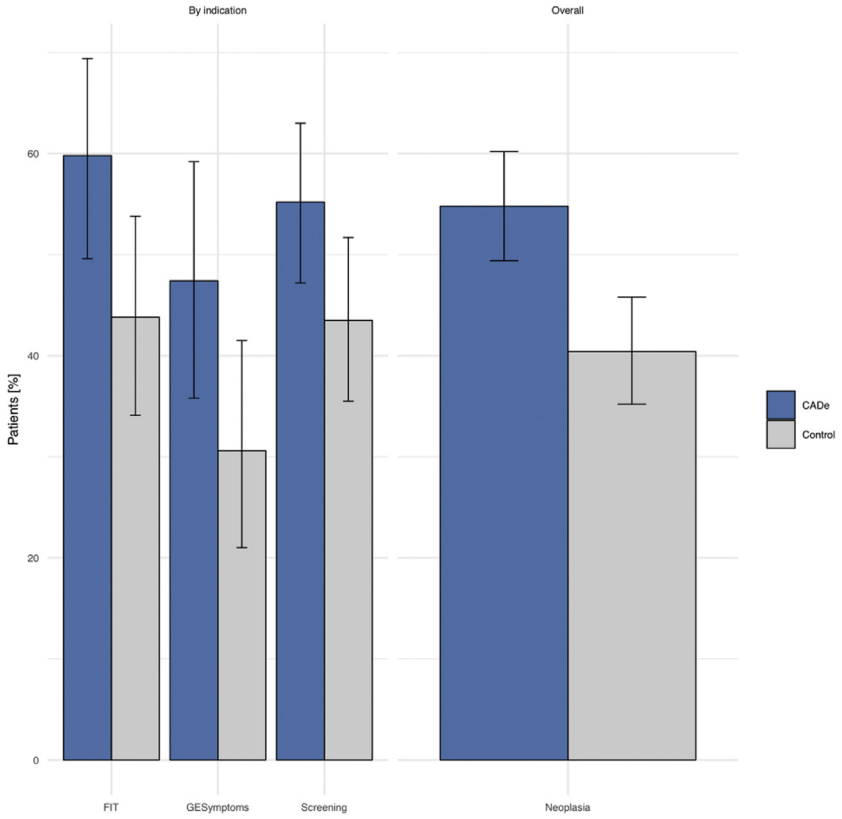
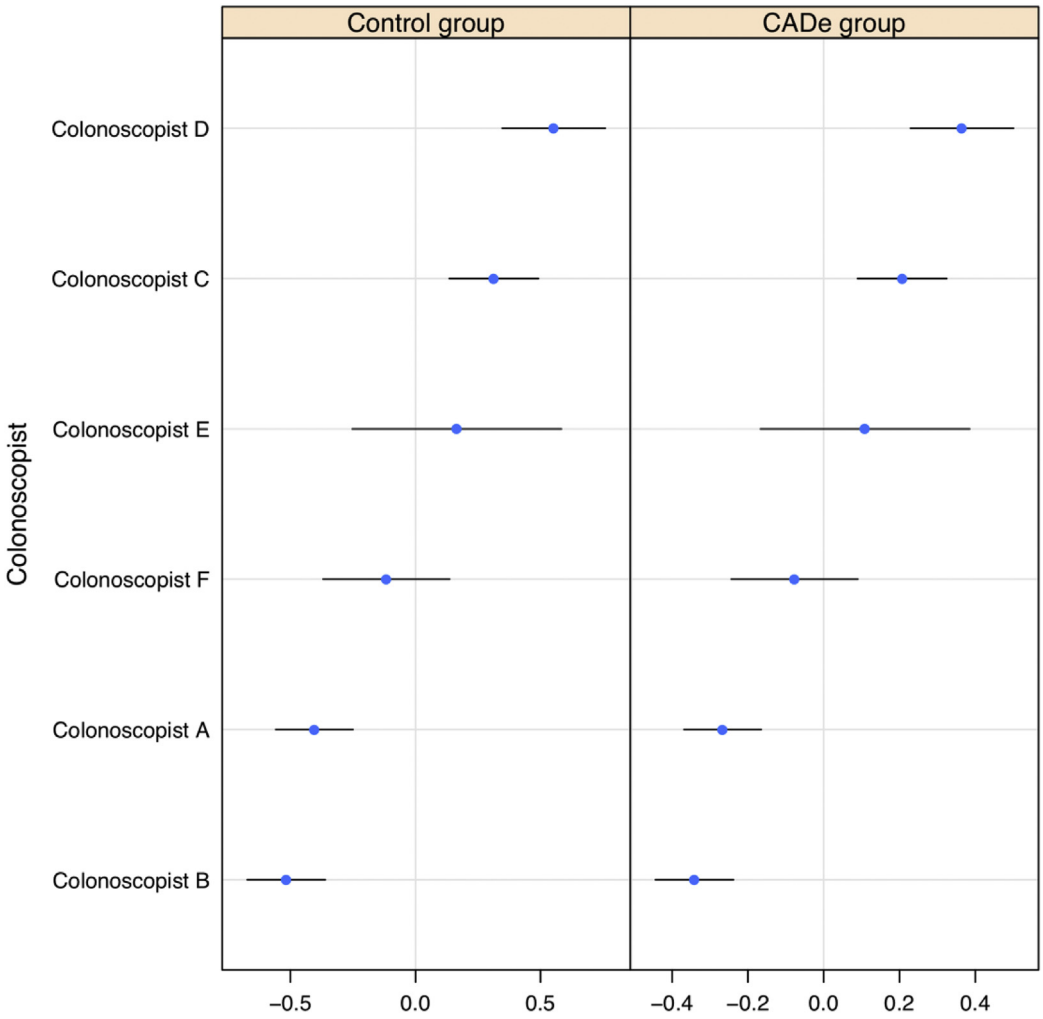
	Control group			CADe group		
	Number of patients	**Number of patients with Adenomas**	**ADR**	**Number of patients**	**Number of patients with Adenomas**	**ADR**
FIT+	105	46	43.8%	102	61	0.598
GE symptoms	85	26	30.6%	76	36	0.474
Screening/Surveillance	154	67	43.5%	163	90	0.552
Total	**344**	**139**	**40.4%**	**344**	**187**	**54.4%**



Supplementary Figure 1. Adenoma ADR by colonoscopy indication.



Supplementary Figure 2. Caterpillar plots showing the "random-effects" (ie, the differences in the ADR of a colonoscopist and the mean ADR level in the logit scale) for CADe and control group. Analysis by using a random-effect model indicated that there was significant variability in ADR between colonoscopists ($P = .01$). According to the model, ADR was significantly higher in the CADe group than control group. The spread in performance levels (average distance from the mean ADR level) in the CADe group was smaller (although not statistically significant) than that in the control group (see Supplementary Figure 1).

Supplementary Table 1. Multivariate Analysis of Adenoma and Advanced Adenoma Detection Rate

	Any adenoma[a]		Advanced adenoma[b]	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Gender		<.001		.065
Women	1		1	
Men	1.31 (1.15–1.46)		1.48 (0.98–2.20)	
Age (y)		<.001		.100
50–62	1		1	
63–74	1.42 (1.27–1.56)		1.42 (0.93–2.10)	
Colonoscopy indication				
FIT+	1		1	
Screening/Surveillance	0.97 (0.78–1.17)	.781	0.33 (0.19–0.55)	<.001
Gastrointestinal symptoms	0.80 (0.59–1.02)	.081	0.43 (0.22–0.77)	.006
Withdrawal time (as continuous variable) (minutes)	1.02 (1.01–1.04)	.002	1.02 (1.00–1.04)	.029
Colonoscopy arm		<.001		
Control	1		1	
CADe	1.30 (1.14–1.45)		1.22 (0.80–1.83)	.334

RR = Risk ratio adjusted for all the variables in the model and for screening center.
[a]Excluding SSA/Ps.
[b]Advanced adenomas were defined as an adenoma of 10 mm or larger, or with at least 20% villous histology or with high-grade dysplasia.

Supplementary Table 2. ADR: PER-PROTOCOL Analysis

Per patient analysis	CADe (n = 335)	Control (n = 331)	Unadjusted RR (95% CI)	*P*-value
Histology				
All adenomas and CRCs	184 (54.9)	135 (40.8)	1.29 (1.14–1.44)§	<.001
Non-advanced adenomas	141 (41.6)	102 (29.9)	1.37 (1.11–1.66)	.003
Advanced neoplasia	43 (12.8)	33 (10.0)	1.28 (0.84–1.91)	.246
Size category[a]				
<10 mm	150 (44.8)	110 (33.2)	1.35 (1.11–1.64)	.003
≥10 mm	34 (10.1)	25 (7.6)	1.35 (0.83–2.21)	.231
Morphology[b]				
Polypoid	124 (37.0)	88 (26.6)	1.35 (1.11–1.61)	.004
Non-polypoid[c]	86 (25.7)	59 (17.8)	1.41 (1.08–1.80)	.015
Location				
Proximal Colon[d]	121 (36.1)	93 (28.1)	1.27 (1.03–1.52)	.027
Distal Colon	107 (31.9)	67 (20.2)	1.51 (1.20–1.88)	<.001

[a]According to the size of the largest neoplastic lesion.
[b]There were 2 cases with missing data in the CADe group.
[c]Polypoid Lesions:Elevated more than 2.5 mm above the mucosal layer: pedunculated (0–1 p), sessile (0–1 s) or mixed (0–1 sp).
[d]Nonpolypoid lesions:Superficial slightly elevated (IIa), flat (IIb), superficial depressed (IIc), and excavated (III) types.

Supplementary Table 3. Histology and Dysplasia of Detected Lesions (Per-Polyp Analysis)

	CADe	Control group
Lesions of any histology and size	**641**	**420**
Polyps ≥10 mm	**47**	**46**
Tubular adenoma	18 (38.3)	19 (41.3)
High-grade dysplasia	5 (10.6)	4 (8.7)
Villous/Tubulovillous	13 (27.7)	9 (19.6)
High-grade dysplasia	7 (14.9)	3 (6.5)
Sessile Serrated Lesion	5 (10.7)[a]	8 (17.4)
Hyperplastic	5 (10.6)	5 (10.9)
Normal mucosa, benign, inflammatory	3 (6.4)	0 (0.0)
Not specified	3 (6.8)	5 (10.9)
Polyps <10 mm	**584**	**371**
Tubular adenoma	304 (52.1)	207 (55.8)
High-grade dysplasia	9 (3.0)	9 (2.4)
Villous/Tubulovillous	8 (1.4)	5 (1.3)
High-grade dysplasia	3 (0.5)	2 (0.5)
Sessile Serrated Lesion	51 (8.8)	24 (6.5)
Hyperplastic	199 (33.9)	120 (32.3)
Normal mucosa, benign, inflammatory	11(1.9)	8 (2.2)
Not specified	11 (1.9)	7 (1.9)
Total number of CRC	10 (1.6)	3 (0.7)

NOTE. Data are n (%).
[a]Of these, 2 cases were SSLs with cytological dysplasia.

Supplementary Table 4. Morphology According to Paris Classification and Colon Location of Detected Adenoma

	CADe	Control Arm
Advanced adenomas	**48**	**42**
Polypoid type[a]	33 (68.8)	26 (61.9)
Nonpolypoid type[b]	15 (31.2)	16 (38.1)
Non-advanced adenomas	**295**	**198**
Polypoid type[a]	171 (58.0)	117 (59.1)
Nonpolypoid type[b]	123 (41.7)	81 (40.9)
Missing	1 (0.3)	0 (0.0)
Colorectal cancers	10	3
Distal	5 (50%)	1 (33.3)
Proximal[c]	5 (50%)	2 (66.7)
Advanced adenomas	**48**	**42**
Distal	26 (50.0)	22 (55.1)
Proximal[c]	22 (50.0)	20 (44.9)
Nonadvanced adenomas	**295**	**198**
Distal	117 (39.7)	67 (33.8)
Proximal[c]	178 (60.3)	131 (66.2)

NOTE. Data are n (%).
[a]Elevated more than 2.5 mm above the mucosal layer: pedunculated (0–1 p), sessile (0–1 s) or mixed (0–1 sp).
[b]Nonpolypoid lesions: superficial slightly elevated (IIa), flat (IIb), superficial depressed (IIc), and excavated (III) types.
[c]Proximal colon (cecum, ascending, transvers colon).

Supplementary Table 5. Analysis of (Per-Polyp) ADR According to Colon Location and Lesion Morphology: Results From a Random-Effect Logistic Model

	Entire colon		Proximal colon		Distal colon		Polypoid adenoma		Nonpolypoid adenoma		Large adenoma	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Colonoscopy arm												
Control	1		1		1		1		1		1	
CADe	1.80 (1.14–2.81)	.012	1.70 (0.95–2.98)	.079	1.41 (1.00–1.98)	.047	1.69 (1.01–2.84)	.045	1.64 (0.92–2.95)	.096	1.00 (0.60–1.62)	.957
Gender												
Women	1		1		1		1		1		1	
Men	2.37 (1.66–3.37)	.002	2.67 (1.49–3.78)	.003	1.14 (0.82–1.60)	.434	2.12 (1.71–3.56)	.004	1.51 (0.84–2.70)	.167	1.66 (1.00–2.78)	.053
Age (y)												
50–62	1		1		1		1		1		1	
63–74	2.93 (1.85–4.10)	<.001	3.12 (2.28–4.53)	<.001	1.17 (0.84–1.63)	.336	2.00 (1.19–3.30)	.010	2.20 (1.42–3.43)	.004	1.17 (0.76–1.91)	.538
TC indication												
FIT+	1		1		1		1		1		1	
Screening/Surveillance	0.64 (0.38–1.05)	.079	0.64 (0.34–1.21)	.179	0.71 (0.50–1.03)	.073	0.60 (0.33–1.05)	.078	0.84 (0.44–1.63)	.621	0.27 (0.32–0.49)	<.001
Symptoms	0.33 (0.20–0.68)	.002	0.46 (0.36–0.78)	.032	0.54 (0.34–0.89)	.013	0.32 (0.16–0.65)	.002	0.71 (0.44–1.64)	.401	0.59 (0.32–1.10)	.098

OR, odds ratio.

Supplementary Table 6. ADR Among FIT+ Patients and by Study Center

	Control patients	CAD-e patients	IRR (95% CI)
ADR	43.8%	59.8%	1.63 (1.28–2.11)
Polypoid adenoma	0.44 (0.94)	0.59 (1.25)	1.50 (1.13–2.07)
Nonpolypoid adenoma	0.30 (0.71)	0.46 (0.96)	1.49 (1.08–2.06)
Proximally located adenomas	0.45 (0.92)	0.60 (1.11)	1.46 (1.05–2.03)
Distally located adenomas	0.27 (0.79)	0.43 (0.79)	1.54 (1.14–2.07)
Small adenomas (<10 mm)	0.62 (1.54)	0.92 (1.42)	1.64 (1.24–2.18)
Large adenomas (≥10 mm)	0.09 (0.35)	0.11 (0.31)	1.07 (0.66–1.74)

	Control Arm		CADe Arm		
CENTER	No. of patients	ADR, n (%)	# of patients	ADR, n (%)	OR [CADe vs. Control]
COMO	42	19 (45.2)	42	25 (59.5)	1.8 (0.8–4.3)
MILANO	171	61 (35.7)	173	85 (49.1)	1.7 (1.1–2.7)*
ROMA	131	59 (45.0)	126	77 (61.1)	1.9 (1.2–3.2)*
Total	344	139 (40.8)	341	187 (54.8)	1.8 (1.3–2.4)*

IRR, incidence rate ratio.
*$P < .05$ for differences between study arms.

Supplementary Table 7. ADR and Mean Number Of Adenomas Per Patient by Colonoscopist (R2–2)

	Control group				CADe group			
Colonoscopist	No. of patients	No. of Patients with adenomas	ADR, %	Adenomas/patient	No. of patients	No. of patients with adenomas	ADR, %	Adenomas/patient
A	84	32	38.1	0.57	86	44	51.2	0.81
B	87	29	33.3	0.52	87	41	47.1	0.74
C	77	36	46.8	0.92	75	45	60.0	1.16
D	54	23	42.6	0.82	51	32	62.7	1.86
E	11	7	63.6	1.27	8	5	62.5	1.00
F	31	12	38.7	0.68	34	20	58.8	0.85
Total	**344**	**139**	**40.4**	**1.20**	**341**	**187**	**54.8**	**1.54**

Supplementary Table 8. SSL Detection Rate (DR) by Colonoscopist

	Control group			CADe group		
	Control group			CADe group		
Colonoscopist	Number of patients	Number of patients with SSL	SSL-DR, %	Number of patients	Number of patients with SSL	SSL-DR, %
A	84	6	7.1	86	9	10.5
B	87	8	9.2	87	11	12.6
C	77	1	1.3	75	2	2.7
D	54	1	1.9	51	0	0.0
E	11	1	9.1	8	2	25.0
F	31	1	3.2	34	0	0.0
Total	344	18[a]	**5.2**	341	24[b]	**7.0**

[a]including 16 patients with synchronous neoplastic lesions.
[b]including 17 patients with synchronous neoplastic lesions.