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Impact of Artificial Intelligence for Detection of Precancerous Colonic Lesions in a Fecal Immunochemical Blood Test-Based Organized Screening Program in Italy: A Randomized Control Trial

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ABSTRACT

Background: The fecal immunochemical test (FIT) is widely implemented as a first-line tool in organized colorectal cancer (CRC) screening programs, including Italy. Following a positive FIT, colonoscopy is recommended. Computer-aided detection (CADe) systems have the potential to enhance adenoma detection, particularly in FIT-positive populations where identifying advanced adenomas is critical for cancer prevention. This study evaluated the diagnostic performance of CADe-assisted colonoscopy versus standard colonoscopy (SC) in a FIT-based screening cohort.

Methods: In this multicenter, randomized controlled trial, patients with a positive FIT result were randomized to undergo either CADe-assisted or standard colonoscopy. The primary endpoint was the advanced adenoma detection rate (AADR). Secondary endpoints included overall adenoma detection rate (ADR), adenomas per colonoscopy (APC), and mean withdrawal time (WT).

Results: Of 1077 patients enrolled, 68 were excluded due to inadequate bowel preparation, leaving 1009 patients for analysis (CADe: $n = 506$; SC: $n = 503$). AADR was comparable between the groups (21.3% vs. 20.5%, $p = 0.794$). However, CADe significantly improved ADR (67.6% vs. 59.8%, $p = 0.012$) and APC (1.82 ± 2.12 vs. 1.34 ± 1.81, $p < 0.001$). Mean WT was longer in the CADe group (17.10 ± 8.28 min vs. 16.13 ± 8.28 min, $p = 0.016$).

Conclusions: In a FIT-based organized CRC screening setting, CADe did not enhance detection of AADR with a modest increase in withdrawal time. NCT04441580.

Abbreviations: (S)AE, (severe) adverse events; AADR, advanced adenoma detection rate; ADR, adenoma detection rate; AI, artificial intelligence; APC, adenoma per colonoscopy; BBPS, Boston bowel preparation scale; CADe, Computer-aided detection; CI, confidence interval; CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; FIT, fecal immunochemical test; ITT, intention-to-treat; mITT, modified intention-to-treat; PDR, polyp detection rate; PPC, polyp per colonoscopy; RCT, randomized controlled trial; SC, standard colonoscopy; SSLDR, sessile serrated lesion detection rate; WT, withdrawal time.

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Key Summary

- Summarise the established knowledge on this subject
  - FIT-based CRC screening programs reduce mortality; colonoscopy after positive FIT is the standard follow-up.
  - Colonoscopy effectiveness is limited by adenoma miss rates, even for advanced lesions.
  - AI-based CADe systems improve adenoma detection in average-risk populations, but evidence in FIT-positive cohorts is inconsistent.
- What are the significant and/or new findings of this study?
  - In a large RCT (n = 1009), CADe did not improve advanced adenoma detection rate (AADR).
  - CADe significantly increased overall ADR and APC, indicating more adenomas per patient were found.
  - Withdrawal time was modestly longer with CADe (~1 min) but not clinically meaningful.
  - Safety profile was preserved, with no increase in unnecessary resections or adverse events.

1 | Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, with an estimated number of more than 1.9 million new cases and 904,000 deaths reported in 2022 [1]. The implementation of organized screening programs aimed at early detection and removal of precancerous lesions has played a key role in reducing this burden. In Italy, a biennial fecal immunochemical test (FIT) is offered to individuals aged 50–69 years (extended to 74 in some regions), with colonoscopy recommended following a positive FIT result.

Colonoscopy remains the gold standard for detecting and removing precancerous colonic lesions [2]; however, its effectiveness is limited by the adenoma miss rate (AMR). Tandem colonoscopy studies report an AMR of 26% for any adenoma, 9% for advanced adenomas, and 27% for serrated polyps [3]. Missed lesions contribute to interval CRC, especially in this high-risk population, emphasizing the need for strategies to enhance adenoma detection rate (ADR), and advanced adenoma detection rate (AADR). Notably, in FIT-positive screening populations, higher ADRs have been inversely associated with the risk of post-colonoscopy CRC [4].

However, in FIT-positive colonoscopies, evidence is inconclusive, with studies reporting inconsistent effects of CADe on AADR and ADR in this high-risk group [5–7]. To date, only two studies have assessed CADe implementation in established FIT-based screening programs, yielding conflicting results regarding its impact [8, 9].

To address the existing inconsistencies in the literature, we designed a randomized multicenter control trial (RCT) aimed to evaluate the diagnostic yield of CADe-assisted colonoscopy compared to standard colonoscopy (SC) in a FIT-based organized CRC screening program.

2 | Materials and Methods

2.1 | Study Design

This multicenter, two-arm, RCT was conducted at three endoscopy centers in Italy: Fondazione Poliambulanza hospital (Brescia), Policlinico Gemelli university research center (Rome) and S. Orsola-Malpighi hospital (Bologna) from March 2020 to December 2023. The study adhered to the principles of Good Clinical Practice and the Declaration of Helsinki. Ethical approval was granted by the Local Ethics Committee in March 2020 (NP 3616), and the trial was registered at ClinicalTrials.gov (NCT04441580). The study follows the CONSORT guidelines for reporting randomized controlled trials.

Consecutive FIT-positive patients referred for colonoscopy within an organized CRC screening program were enrolled. The program offered biennial FIT to men and women aged 50–74 years (cutoff 20 μg/g). Exclusions included inability or refusal to consent and inadequate discontinuation of antiplatelet or anticoagulant therapy contraindicating polypectomy.

2.2 | Randomization

Patient allocation into the two study groups was performed using simple single-stage randomization through a random number generator by a study member. In detail, an allocation list for the two groups in a 1:1 ratio was generated before the start of the procedure, using an automatic random number generator with only two categories (the group labels). This allowed a predefined allocation list to be created in advance. Consecutive patients who met inclusion criteria were enrolled and then sequentially allocated to one of the two study arms, according to the predefined allocation list. Endoscopists, patients and the statistician were not blinded to the study allocation.

2.3 | Artificial Intelligence

The CADe-assisted colonoscopy system used in this randomized controlled trial is an artificial intelligence-based real-time image analysis device (GI Genius; Medtronic, Dublin, Ireland). The system receives digital images directly from the endoscopy processor and performs real-time analysis to identify suspected colorectal polyps. It was trained and validated using video data of 2684 histologically confirmed polyps from 840 patients, achieving a per-lesion sensitivity of 99.7% [10]. When the system identifies a potential abnormality, it highlights the region by drawing a green box directly onto the live endoscopic image.

2.4 | Study Procedures

Colonoscopies were performed by experienced endoscopists (> 2000 examinations). All endoscopic procedures were performed with a high-definition Olympus EVIS X1 (Olympus PCF/CF

−190; Olympus Co., Tokyo, Japan) and were recorded and stored in the hospital database. Bowel preparation was given in accordance with ESGE guidelines [11] and cleanliness was scored using the Boston Bowel Preparation Scale (BBPS) [12].

Both CADe and SC were performed according to standard local protocols for patient management and monitoring. All colonoscopies were performed using procedural sedation, which was prescribed by the endoscopist according to the patient clinical conditions and sedation protocols. Endoscopic landmarks (i.e., ileocecal valve, appendicular orifice) were clearly photographed. Withdrawal time was measured using a stopwatch. A minimum of 6 min of withdrawal time from the cecum, excluding interventions (biopsies/polyp resections), was required.

The CADe device was activated after cecal intubation. During the withdrawal phase, the CADe system highlighted detected lesions with a virtual square overlay on the same monitor used for the procedure, accompanied by a beeping sound to draw attention to the findings. Vital staining and virtual chromoendoscopy were not allowed for polyp detections. Polyps were described reporting estimated size, colonic location, and morphological classification using Paris classification systems [13]. Resected polyps were divided in jars, stocked in 10% buffered formalin containers, and sent for histopathological examination, according to the Vienna criteria, performed by pathologists [14]. Patients were followed up for adverse events 30 days after the procedure.

2.5 | Outcomes Measures and Aims

AADR was the primary aim of this study defined as the percentage of patients with at least one adenoma ≥ 10 mm, high-grade dysplasia, and/or villous histology. As secondary endpoints were considered: ADR, calculated as the percentage of patients with at least one histologically proven adenoma, Polyp Detection Rate (PDR), Polyp Per Colonoscopy (PPC), Adenoma Per Colonoscopy (APC), Sessile serrated Lesion Detection Rate (SSLDR), Adenoma + Sessile Serrated Lesion Per Colonoscopy (ASPC), Corrected Withdrawal Time (WT), Polyps size and locations, and (Severe) adverse events (S)AEs up to 30 days post-procedure. Endpoint definitions are summarized in Table 1S. Hyperplastic or inflammatory polyps and normal mucosa were grouped into non-neoplastic lesions group for statistical analysis.

All the outcomes were assessed and compared between the two-arms to detect any statistically significant improvement.

2.6 | Statistical Analysis

Descriptive statistics per patient were provided in terms of mean ± standard deviation (SD) for the continuous variables; and in terms of frequency and percentage (%) or rate for the categorical variables. Group comparisons were assessed by Student t-test or non-parametric Mann-Whitney test for continuous variables and Chi-squared test or test for proportion for categorical variables. Intention-to- treat (ITT) analysis included all randomized patients while modified intention to treat (mITT) analysis excluded patients with a BBPS < 2 in any segment and/or missed cecal intubation and/or with a withdrawal time < 6 min.

Per-lesion analyses were instead evaluated using generalized linear mixed models (for Poisson or Binomial data distributions) to manage the clustering effect of lesions within the same subject (patients specified as random effect), while the study group, polyp size, polyp colonic location and morphological classification using Paris classification systems were considered as fixed factors. The *p*-values regarding the analyses stratified by polyp size were obtained from the post hoc interaction effect, specifically the interactions between group and size.

Univariable and multivariable logistic regression models were performed to assess the predictors of the outcomes. In the univariable logistic model, the associations between study group (standard colonoscopy vs. CADe-assisted colonoscopy), socio-demographic and clinical features with the outcomes were assessed by applying one model for each variable (as single predictor). The multivariable logistic model was applied for assessing the potential confounding effect of socio-demographic and clinical variables in the analysis of the association between study group and the primary outcome. The results of logistic models were reported in terms of Odds Ratio (OR) and corresponding 95% confidence interval (95% CI).

Confidence intervals that include "1" indicate not-significant association. Analyses were performed by statistical software R (URL https://www.R-project.org/; R version 4.4.0) and using the following package: *lme4*, *lmerTest*, *multcomp* for carrying out the generalized linear mixed model. The significance level was set at 0.05. Details about the sample size are reported in Appendix 1 in Supporting Information Sl.

3 | Results

3.1 | Study Population

A total of 1100 patients were assessed for eligibility. Of these, 23 individuals were excluded due to screening failure. Subsequently, 1077 patients were randomized into two groups: 537 in the CADe group and 540 in the control group, and they were all included in the ITT analysis. After excluding 68 patients due to inadequate bowel cleansing, a mITT was conducted on 1009 patients: 506 patients in the CADe group and 503 patients in the SC group (Figure 1). Baseline demographic and clinical characteristics of the patients included in both groups were similar, as detailed in Table 1 and Supporting Information S1: Table 2S.

3.2 | Per-Patient Analysis

On mITT, the number of colonoscopies with at least one advanced adenoma found was 108/506 in the CADe group versus. 103/503 in SC (21.3% vs. 20.5%, $p = 0.794$). ADR was

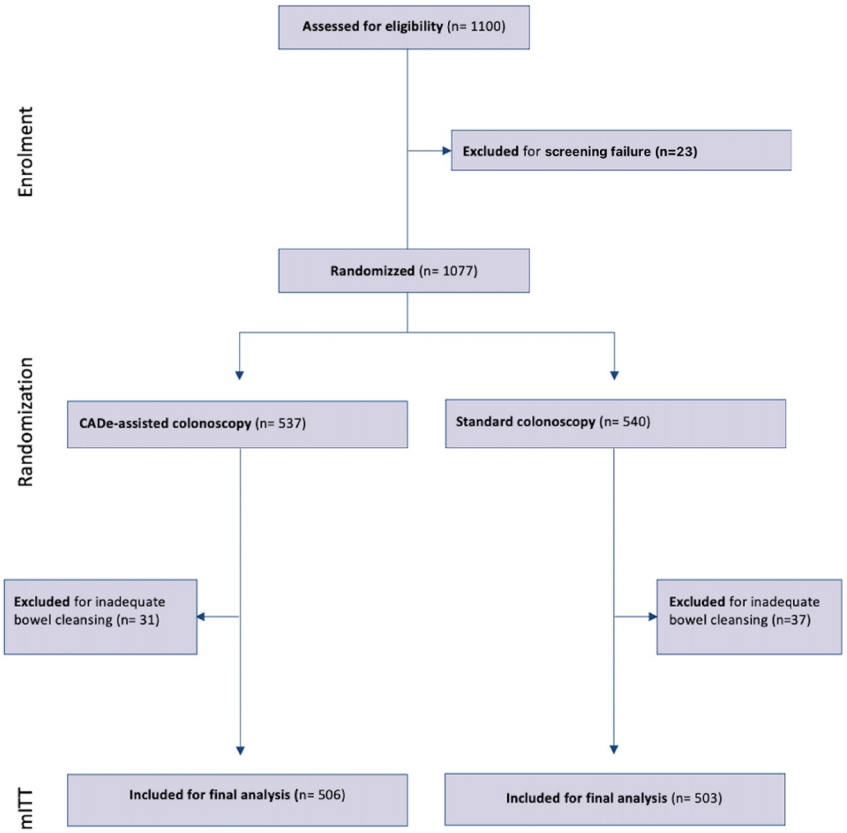

FIGURE 1 | CONSORT-AI flow diagram.

TABLE 1 | Baseline patient characteristics at mITT.

	CADe colonoscopy $n = 506$	Standard colonoscopy $n = 503$	p value
Sex, *n* (%)			0.976
Male	248 (49.0%)	248 (49.3%)	
Female	258 (51.0%)	255 (50.7%)	
Mean age, y (SD)	62.8 (7.02)	62.0 (7.31)	0.079
Screening round (n, % first round)	36 (7.1%)	37 (7.4%)	0.979
Bowel preparation regimen, *n* (%)			0.084
1 L PEG + ascorbate + sodium sulfate	393 (77.7%)	361 (71.8%)	
2 L PEG + ascorbate	61 (12.1%)	65 (12.9%)	
4 L PEG	39 (7.7%)	61 (12.1%)	
Other laxatives	13 (2.6%)	16 (3.2%)	
Timing of laxatives, *n* (%)			0.345
Day before	59 (11.7%)	73 (14.5%)	
Split dose	421 (83.2%)	401 (79.7%)	
Same day	26 (5.1%)	29 (5.8%)	
Boston Bowel preparation scale, *n* (%)			0.177
BBPS = 6	143 (28.3%)	157 (31.2%)	
BBPS = 7–8	41 (8.1%)	54 (10.7%)	
BBPS = 9	322 (63.6%)	292 (58.1%)	

Abbreviations: BBPS: Boston Bowel Preparation Scale, CADe: Computer-aided detection.
#: for categorical variables *p*-values were carried out by chi-squared test; for continuous/numerical variables *p*-values were carried out by Student t-test.

342/506 in the CADe group and 301/503 in SC (67.6% vs. 59.8% $p = 0.012$). Compared to standard colonoscopy, CADe increased ADR by an absolute 7.8% points, corresponding to a 13% relative increase. CADe also significantly increased PDR (401/506 [79.2%] vs. 350/503 [69.6%], $p < 0.001$), PPC (2.62 ± 2.65 vs. 2.04 ± 2.47, $p < 0.001$), APC (1.82 ± 2.12 vs. 1.34 ± 1.81, $p < 0.001$) and ASPC (2.09 ± 2.27 vs. 1.63 ± 2.05, $p < 0.001$). There was no significant difference in the SSL detection rate (91/509 [18.2%] vs. 91/103 [18.3%], $p = 1.000$) between the CADe and standard colonoscopy groups. The Withdrawal Time (WT), characterized by a mean of 17.10 ± 8.28 in CADe, exhibited statistically significant distinctions in comparison to the control group (16.13 ± 8.28 in SC), although the absolute difference (57 s) was clinically irrelevant. No severe adverse events were reported during the study period. Results are summarized in Table 2.

On ITT analysis, there was no significant difference in AADR (110/537 [20.1%] vs. 104/540 [18.9%], $p = 0.745$) and SSL detection rate (92/537 [17.3%] vs. 92/540 [17.2%], $p = 0.816$) between the CADe and standard colonoscopy groups. However, CADe significantly increased ADR (345/537 [64.2%] vs. 305/540 [56.5%], $p = 0.033$), PDR (405/537 [75.6%] vs. 354/540 [65.6%], $p < 0.001$), PPC (2.62 ± 2.64 vs. 2.04 ± 2.47, $p = < 0.001$) and APC (1.82 ± 2.11 vs. 1.35 ± 1.80, $p < 0.001$). Results are reported in Supporting Information S1: Table 2S.

3.3 | Per-Polyp Analysis

A total of 2351 polyps (Table 3) were identified, removed, and analyzed of whom 1597 were adenomas (922 CADe [69.6%] vs. 675 SC [65.8%], $p = 0.001$), 277 sessile serrated lesions (134 CADe [10.1%] vs. 143 SC [13.9%], $p = 0.506$), 11 colorectal adenocarcinoma (6 CADe [0.5%] vs. 5 SC [0.5%], $p = 0.901$) and 466 non-neoplastic lesion (263 CADe [19.8%] vs. 203 SC [19.8%], $p = 0.632$). Among the adenomas, 1112 were smaller than 5 mm (675 CADe [73.2%] vs. 437 SC [64.7%], $p = 0.061$).

Considering the adenoma location (Table 4), 1037 were found in the proximal colon (611 CADe [58.9%] vs. 426 SC [41.1%], $p < 0.001$). CADe detected a higher number of adenomas ≤ 5 mm in the proximal colon compared to SC (493 [58.7%] vs. 315 [49.5%]), although the difference in percentage did not reach the significance ($p = 0.150$).

Among sessile serrated lesions, no differences were found between the groups. Results are summarized in Table 4.

Similar results have been found at ITT analysis and are reported in Supporting Information S1: Table 3S.

3.4 | Univariable and Multivariable Logistic Regression Analysis

Regression analysis was performed to identify predictors of adenoma. The potential examined predictors of the dichotomous dependent variable adenoma detection (AD) were group (CADe vs. SC), age, sex and presence of symptoms (diarrhea, weight loss, anemia, rectal bleeding, constipation and abdominal pain).

In the univariable analysis, group, age and sex resulted as significant predictors for AD: in the CADe group, the probability to detect an adenoma was 39% higher than the probability to not detect it (OR = 1.39, 95%CI [1.08, 1.81]). Similarly, for each additional age-year, the probability to detect an adenoma increased by 5% (OR = 1.05, 95%CI [1.03, 1.07]), and for a 10-year change, the probability to detect an adenoma was 61% higher. With respect to sex, being female (with respect to being male) decreased by 52% the probability to detect an adenoma (OR = 0.48, 95% CI [0.37, 0.63]). Conversely, the presence of

TABLE 2 | Endpoint measurements among the study population in mITT analysis.

	CADe colonoscopy $n = 506$	Standard colonoscopy $n = 503$	95% CI %difference or Cohen's d effect size[a]	p value
AADR n (%)	108 (21.3%)	103 (20.5%)	[−4.3%, 6.1%]	0.794
ADR n (%)	342 (67.6%)	301 (59.8%)	[1.6%, 13.9%]	0.012
PDR n (%)	401 (79.2%)	350 (69.6%)	[4.1%, 15.2%]	< 0.001
PPC mean ± SD	2.62 ± 2.65	2.04 ± 2.47	$d = 0.23$	< 0.001
APC mean ± SD	1.82 ± 2.12	1.34 ± 1.81	$d = 0.24$	< 0.001
ASPC mean ± SD	2.09 ± 2.27	1.63 ± 2.05	$d = 0.21$	< 0.001
SSLDR n (%)	91 (18.2%)	91 (18.3%)	[−4.9%, 4.7%]	1000
Withdrawal time min (SD)	17:10 ± 8:28	16:13 ± 8:28	$d = 0.09$	0.016
(S)AE n (%)	0	0	—	—

Abbreviations: (S)AE: Severe adverse events, AADR: advanced adenoma detection rate, ADR: Adenoma Detection Rate, APC: Adenoma Per Colonoscopy, ASPC: Adenoma + Sessile Serrated Lesion Per Colonoscopy, BBPS: Boston Bowel Preparation Scale, CADe: Computer-aided detection, CI: confidence interval, PDR: Polyp Detection Rate, PPC: Polyp Per Colonoscopy, SSLDR: Sessile Serrated Lesion Detection Rate.

[a]95% CI of the percentage differences were performed for differences in proportions between the two study groups while the Coehn's d effect size was performed for continuous variables.

&: p-values were carried out by test for proportion (for rate variables).

$: p-values were carried out by Mann-Whitney test for continuous/count variables.

TABLE 3 | Per-lesion analysis. Characteristics of polyps resected in mITT analysis.

Polyps, *n* (%)	CADe[c] 1325 (56.4%)	Standard colonoscopy 1026 (43.6%)	95% CI %difference[d] [0.098, 0.156]	*p*-value 0.015
Paris Classification, *n* (%)[&]				
ls	1051(79.3%)	771 (75.1%)	[0.3%, 7.7%]	0.041
lp	81 (6.1%)	78 (7.6%)	[−3.6, 0.7%]	0.099
IIa, IIb, IIc	172 (13.0%)	163 (15.9%)	[−5.8%, 0.1%]	0.593
LST	14 (1.1%)	13 (1.2%)	[−1.1%, 0.7%]	0.825
Ulcerated neoplasms	1 (0.0%)	1 (0.0%)	[−0.2%, 0.2%]	0.859
Histology, *n* (%)				
Adenoma	922 (69.6%)	675 (65.8%)	[0.9%, 7.7%]	0.001
≤ 5 mm	675 (73.2%)	437 (64.7%)	[0.9%, 13.2%]	0.061#
6–9 mm	140 (15.2%)	132 (19.6%)	[−8.2%, 0.5%]	0.556#
≥ 10 mm	104 (11.3%)	106 (15.7%)	[−3.3% 0.1%]	0.108#
Sessile serrated lesion	134 (10.1%)	143 (13.9%)	[−6.6%, 1.1%]	0.506
≤ 5 mm	69 (51.5%)	84 (58.7%)	[−19.7%, 5.2%]	0.989#
6–9 mm	48 (35.8%)	38 (26.6%)	[−2.4%, 20.8%]	1.000#
≥ 10 mm	14 (10.4%)	21 (14.7%)	[−12.7%, 4.3%]	0.962#
Non-neoplastic lesion[a,&]	263 (19.8%)	203 (19.8%)	[−3.2%, 3.4%]	0.632
Colorectal cancer[&]	6 (0.5%)	5 (0.5%)	[−0.6%, 0.6%]	0.901
Size, *n* (%)[&]				
≤ 5 mm	974 (73.5%)	690 (67.3%)	[2.4%, 10.1%]	0.001
6–9 mm	218 (16.4%)	200 (19.5%)	[−6.3%, 0.2%]	0.140
≥ 10 mm	126 (9.5%)	136 (13.3%)	[−6.4%, −1.1%]	0.005
Location, *n* (%)[&]				
Distal colon[c]	485(36.6%)	390 (38.0%)	[−5.4%, 2.6%]	0.478
Proximal colon[b]	840 (63.4%)	636 (62.0%)	[−2.6%, 5.4%]	0.478

Abbreviations: CADe: Computer-aided detection, CI: confidence interval, Ip: peduncolate polyp, Is: sessile polyp, IIa: flat and elevated polyp, IIb completely flat polyp, IIc superficially depressed polyp, LST: lateral spreading tumor.
[a]Hyperplastic or inflammatory polyp or normal mucosa.
[b]Located in the cecum, ascending colon, right colic flexure, or transverse colon.
[c]Located in the left colic flexure, descending colon, sigmoid colon, or rectum.
[d]95% CI of the percentage differences were performed for differences in proportions between the two study groups.
[#]*p*-values were calculated by using mixed models (post-hoc of interaction term: size x group).
[&]*p*-values were calculated by using mixed models on dataset stratified for: Paris classification system, type of lesion (non-neoplastic and cancer), size, colonic location (post-hoc of group term). In some variables, the sum of frequencies may not equal the total due to missing values.

symptoms had no effect on AD (OR = 0.89, 95%CI [0.61, 1.31]). Finally, the effects of group, sex and age on AD were independent across CADe and SC groups: in the multivariable model (with group, age, sex as predictors), the OR of the group (OR = 1.36 95%CI [1.04, 1.77]) remained substantially equal to the OR of the univariable model (Table 4S).

4 | Discussion

In this multicenter, randomized controlled trial conducted within a FIT-based organized colorectal cancer screening program, we found that CADe-assisted colonoscopy, when performed by experienced endoscopists, did not result in a significantly higher detection rate of advanced adenomas compared with conventional colonoscopy. The absence of a significant effect of CADe on increasing AADR in FIT-based organized screening populations has been highlighted in previous studies and in a recent meta-analysis [8, 9, 15]. This may be partly explained by the higher baseline prevalence of precancerous lesions in FIT-positive individuals, which could limit the incremental benefit of CADe [16]. Notably, the AADR achieved by our experienced endoscopists is consistent with benchmarks reported in other studies with similarly experienced practitioners [8, 9, 17]. In contrast, a recent meta-analysis involving broader populations with varying indications have demonstrated that CADe can improve the detection of advanced colorectal neoplasia. However, it is suggested that this benefit is attenuated in FIT-positive patients [18].

Despite the lack of a significant impact of CADe on AADR, it is important to highlight that its use was associated with an absolute increase of 7.8% in ADR and 0.48 in APC, corresponding

TABLE 4 | Per-lesion analysis. Adenoma and Sessile Serrated Lesion sized based on location.

	Proximal colon[a]				Distal colon[b]			
Size, *n* (%)	CADe (*n* = 840)	SC (*n* = 636)	95% CI % difference[c]	*p* value	CADe (*n* = 485)	SC (*n* = 390)	95% CI %difference[£]	*p* value
Adenoma								
≤ 5 mm	493 (58.7%)	315 (49.5%)	[−0.9%, 14.4%]	0.150	182 (37.5%)	122 (31.3%)	[−0.3%, 12.7%]	0.988
6–9 mm	69 (8.2%)	67 (10.5%)	[−5.4%, 0.8%]	0.944	71 (14.6%)	65 (16.7%)	[−7.1%, 3.1%]	0.340
≥ 10 mm	49 (5.8%)	44 (6.9%)	[−3.7%, 1.5%]	0.383	55 (11.3%)	62 (15.8%)	[−9.4%, 0.3%]	0.758
Sessile serrated lesion								
≤ 5 mm	53 (6.3%)	72 (11.3%)	[−8.1%, 1.9%]	0.801	16 (3.3%)	12 (3.1%)	[−2.3%, 2.7%]	0.999
6–9 mm	42 (5.0%)	33 (5.2%)	[−2.6%, 2.2%]	1000	6 (1.2%)	5 (1.3%)	[−1.6%, 1.5%]	1000
≥ 10 mm	13 (1.5%)	19 (2.9%)	[−3.1%, 2.9%]	0.961	1 (0.0%)	2 (0.0%)	[−1.4%, 0.5%]	0.999

[a]Located in the cecum, ascending colon, right colic flexure, or transverse colon.
[b]Located in the left colic flexure, descending colon, sigmoid colon, or rectum. *p*-values were carried out by test for proportion.
[c]95% CI of the percentage differences were performed for differences in proportions between the two study groups.

to relative increases of 13.4% and 35.8%, respectively. Given that ADR is inherently higher in FIT-positive populations compared with other colonoscopy indications, current guidelines recommend a target ADR of ≥ 40% in FIT-based screening programs [19, 20]. In our study, the baseline ADR among experienced endoscopists was already at 59.8%; nonetheless, the use of CADe led to a statistically significant further increase in ADR. Adenoma removal remains a cornerstone of colorectal cancer prevention, and ADR has been shown to be inversely associated with the risk of interval colorectal cancer in FIT-positive colonoscopies [21, 22]. These findings support the potential value of implementing CADe where further improvements in ADR may contribute to reducing the incidence of post-colonoscopy colorectal cancer (PCCRC). According to a recent systematic review, in direct colonoscopy screening, increasing the ADR beyond a certain cut-off—likely around 37%—does not appear to further reduce the risk of PCCRC [23]. However, this relationship has not yet been established for FIT-based programmes; therefore, pursuing higher ADR targets may still be warranted. In a recent microsimulation model, the application of CADe during FIT-positive screening colonoscopies may prevent approximately five colorectal cancer cases per 10,000 individuals over a 10-year period, although this estimate is currently supported by low certainty of evidence [16].

Although the ADR is widely recognized as a key quality indicator for colonoscopy, it has inherent limitations—most notably the "one and done" phenomenon, wherein an endoscopist may cease careful inspection after detecting a single adenoma. ADR does not account for the total number of adenomas identified during a procedure and therefore does not distinguish between endoscopists with varying detection per colonoscopy [24]. To address this limitation, APC—defined as the total number of adenomas detected divided by the number of screening colonoscopies performed—has been proposed as a complementary quality metric. Notably, the use of CADe was associated with a significantly higher APC compared with standard colonoscopy in our study. Despite the conceptual relationship between ADR and APC, existing studies have not consistently demonstrated a strong correlation between the two measures, underscoring the need for further investigation into their respective roles and combined utility in evaluating colonoscopy quality [25, 26].

However, even with the potential for improved detection, concerns have emerged regarding the clinical relevance of increasing the identification of diminutive adenomas, particularly in high-ADR settings. Non-advanced lesions are associated with a low risk of malignant transformation and follow a slow adenoma–carcinoma sequence, thereby limiting their clinical significance. Enhanced detection of such lesions—especially with the use of CADe—may inadvertently lead to an increase in surveillance colonoscopies, which are typically guided by polyp number, size, and histology [27]. Microsimulation models have suggested that widespread implementation of CADe could result in a higher volume of surveillance procedures within a decade following the index colonoscopy, both in average-risk populations and in those undergoing FIT-based screening [16, 28]. Another concern regarding the use of artificial intelligence in colonoscopy is the potential increase in unnecessary polypectomies of non-neoplastic lesions, which may in turn elevate the risk of adverse events such as post-polypectomy bleeding [14, 26]. However, our findings suggest that the implementation of CADe within a CRC screening program does not lead to a significant increase in the resection of non-neoplastic lesions, nor does it result in a higher rate of procedure-related complications. These results support the safety profile of CADe in this context.

In this RCT, withdrawal time was longer in the CADe group compared with the standard colonoscopy group (17.10 ± 8.28 min vs. 16.13 ± 8.28 min). However, the absolute difference of 57 s is unlikely to be clinically meaningful. These findings are consistent with results from a recent meta-analysis, which also reported a modest but statistically significant increase in WT associated with CADe-assisted colonoscopy [18].

This study has several notable strengths. It features a large sample size and was conducted within the structured context of a FIT-based organized colorectal cancer screening program,

involving a well-balanced study population. The multicenter design further enhances the generalizability of the findings across diverse clinical settings. However, several limitations should be acknowledged. The primary limitation is the potential influence of the Hawthorne effect—namely, the possibility that endoscopists modified their performance due to awareness of being observed, which may have led to an overestimation of CADe efficacy or an underestimation of performance in the standard colonoscopy group [29]. Additionally, the high ADR observed in the control group, along with the inclusion of only expert endoscopists, may limit the applicability of the results to broader clinical practice. Nevertheless, the baseline ADR aligns with current guideline recommendations, supporting the validity of the study. Another limitation is the extended recruitment period, which spanned more than three years and was significantly impacted by the COVID−19 pandemic. Finally, although false-positive and false-negative rates are important metrics for evaluating the diagnostic accuracy of CADe systems, such data could not be collected in this study.

In conclusion, in this multicenter RCT, CADe-assisted colonoscopy did not lead to an increase in the detection of advanced adenomas in a FIT-positive screening population. However, it was associated with significant improvements in both ADR and APC, with a modest increase in withdrawal time. These findings underscore the potential of CADe to enhance overall detection performance, though its impact on clinically meaningful outcomes in this high-risk cohort remains uncertain. Further research is warranted to better quantify the balance of benefits and potential burdens associated with the implementation of CADe in FIT-based screening programs.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Individual de-identified patient data that underlie the results reported in this article will be made available to investigators whose proposed use of the data has been approved by the corresponding author and with a signed data access agreement. Access to the data is granted solely for the purposes outlined in the approved proposal. For inquiries or proposals, please contact the corresponding author. Interested parties seeking access or inquiries regarding the AI system and/or its code can contact the manufacturer Medtronic Inc. (Dublin, Ireland) for further information.

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