Efficacy of a computer-aided detection system in a fecal immunochemical test-based organized colorectal cancer screening program: a randomized controlled trial (AIFIT study)

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ABSTRACT

Background Computer-aided detection (CADe) increases adenoma detection in primary screening colonoscopy. The potential benefit of CADe in a fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening program is unknown. This study assessed whether use of CADe increases the adenoma detection rate (ADR) in a FIT-based CRC screening program.

Methods In a multicenter, randomized trial, FIT-positive individuals aged 50–74 years undergoing colonoscopy, were randomized (1:1) to receive high definition white-light (HDWL) colonoscopy, with or without a real-time deep-learning CADe by endoscopists with baseline ADR > 25%.

The primary outcome was ADR. Secondary outcomes were mean number of adenomas per colonoscopy (APC) and advanced adenoma detection rate (advanced-ADR). Subgroup analysis according to baseline endoscopists’ ADR (≤ 40%, 41%–45%, ≥ 46%) was also performed.

Results 800 individuals (median age 61.0 years [interquartile range 55–67]; 409 men) were included: 405 underwent CADe-assisted colonoscopy and 395 underwent HDWL colonoscopy alone. ADR and APC were significantly higher in the CADe group than in the HDWL arm: ADR 53.6% (95%CI 48.6%–58.5%) vs. 45.3% (95%CI 40.3%–50.45%); RR 1.18; 95%CI 1.03–1.36); APC 1.13 (SD 1.54) vs. 0.90 (SD 1.32; P = 0.03).

No significant difference in advanced-ADR was found (18.5% [95%CI 14.8%–22.6%] vs. 15.9% [95%CI 12.5%–19.9%], respectively). An increase in ADR was observed in all endoscopist groups regardless of baseline ADR.

Conclusions Incorporating CADe significantly increased ADR and APC in the framework of a FIT-based CRC screening program. The impact of CADe appeared to be consistent regardless of endoscopist baseline ADR.
Introduction

Fecal immunochemical test (FIT) followed by a colonoscopy has demonstrated a reduction in incidence and mortality from colorectal cancer (CRC), and has been implemented as the preferable population-based strategy for CRC screening in Europe [1].

As the risk of interval cancer has been associated with the adenoma detection rate (ADR), optimizing adenoma detection is crucial to increasing the effectiveness of CRC screening programs. For this purpose, new techniques and many technological devices that increase mucosal contrast and maximize mucosal exposure have been widely investigated over past decades, but their impact on ADR has been inconsistent across studies [2, 3].

Recently, computer-aided detection (CADe) systems based on artificial intelligence (AI) have been gaining increasing attention [4–6]. AI-based systems have made significant progress owing to the development of deep neural networks and machine learning algorithms, especially in the area of computer vision. Convolutional neural networks (CNNs) are a class of deep neural networks that are highly effective in image and video analysis. Initial studies consistently showed that CNN-based systems effectively support the endoscopist in evaluating colonoscopy images, making the identification of colonic polyps easier [7–14].

Most available studies on CADe are based on a primary screening and/or diagnostic setting, but no study has specifically looked at the potential benefit of CADe in FIT-based screening programs. This is relevant for two reasons: first, the FIT-positive population is characterized by a very high ADR due to enrichment with adenomas filtered out by the test itself. Second, before implementing a strategy in an organized population-based program, additional evidence is needed.

We designed a prospective randomized controlled trial to assess whether the use of a CADe system affects the detection of adenomas in a FIT-based organized CRC screening program.

Methods

Centers and patients

This prospective randomized controlled trial was conducted in five open-access endoscopy centers in Italy. The institutional review board of all participating centers approved the protocol (Coordinating Center Approval number: 298/2020 on 22/09/2020 by Comitato Etico dell’Insubria, Regione Lombardia, ASST Sette Laghi). All patients provided their written informed consent. The study was planned and is reported according to CONSORT-AI guidelines [15].

Study setting and included patients

In the CRC screening program, residents aged 50–74 years with an average risk for CRC are invited via mail every 2 years to perform a single FIT. The OC-Hemodia latex agglutination test, developed with the OC-sensor system (Eiken Co., Ltd, Tokyo, Japan), is used. The cutoff for test positivity is 20 μg Hb/g feces (100 ng Hb/mL buffer). Individuals are notified of their results by mail and people with a negative FIT are advised to repeat the screening test 2 years later. Individuals with a positive screening test (FIT+) are contacted by telephone and invited for a colonoscopy.

FIT+ individuals who underwent colonoscopy were invited to participate in the current study. Individuals were excluded from the study if they were not eligible for the screening program (i.e. colonoscopy performed in the previous 5 years, personal history of CRC, colonic adenomas, inflammatory bowel disease, severe comorbidity), or had previous colonic resection, antithrombotic therapy precluding polyp resection and pathology assessment, inadequate bowel preparation (defined as a Boston Bowel Preparation Scale [BBPS] score <2 in at least one colonic segment), cecal intubation not achieved or patient refusal to give informed written consent.

Study design

Eligible patients were randomized (1:1) into two arms. Randomization was based on a computer-generated randomized block sequence (10 patients), stratified per center; the endoscopist was blinded to the block size. Allocation was concealed and kept in a sealed envelope, which was opened prior to starting the procedure.

In the control arm, patients underwent standard high definition white-light (HDWL) colonoscopy. In the intervention arm, all patients received HDWL colonoscopy examination with the assistance of a CADe system (see details below), which was switched on in both insertion and withdrawal phases.

The study was single blinded: the patient was blinded, but the endoscopist was aware of the randomization arm as both the endoscopic image and the CADe output were simultaneously displayed on the same screen.

Study aims and outcome measures

The primary aim was to assess whether the use of a CADe system significantly affects the detection of adenomas in FIT+ patients undergoing colonoscopy. The main study outcome was ADR, defined as the proportion of patients with at least one adenoma detected. Secondary outcomes were the number of adenomas per colonoscopy (APC; defined as the number of adenomas divided by the number of colonoscopies performed), the advanced-ADR (defined as the proportion of patients with at least one advanced adenoma detected), sessile serrated lesion (SSL) detection rate, proximal/distal adenoma detection rate, and polypoid/nonpolypoid adenoma detection rate.

We also planned an exploratory subanalysis according to endoscopists’ baseline ADR (defined as endoscopist’s ADR in FIT+ screening procedures performed in the 12 months prior to the study start). As the overall baseline ADR was 42.8% (range 30.0%–55.0%), participating endoscopists were stratified into three groups according to baseline ADR: group 1 ADR ≤40%; group 2 ADR 41%–45%; group 3 ADR ≥46%.
Colonscopy procedure

All procedures were performed using the ELUXEO 7000 endoscopy platform (including video processor ELUXEO VP-7000 and light source ELUXEO BL-7000; Fujifilm Co., Tokyo, Japan).

Bowel preparation consisted of a split regimen of a low-volume solution, according to the local protocol. The quality of bowel cleansing was recorded according to the BBPS [16]. Colonoscopies were performed under conscious sedation, according to local sedation protocols. Intubation time and inspection time during withdrawal were measured using a stop-watch, pausing during therapeutic interventions and washing. A withdrawal time of at least 6 minutes (2 minutes in each colonic segment: right, transverse, and left colon) was mandatory in both arms. Polyp location was defined as "proximal" if polyps were located in the cecum, ascending colon, or transverse colon, and as "distal" in the remaining cases. The polyp size (estimated by comparison with an open forceps or snare) was defined as diminutive (≤5 mm), small (6–9 mm), or large (≥10 mm). The polyp morphology was described according to the Paris classification [17]; pedunculated, sessile, or semipedunculated polyps were grouped as "polypoid," otherwise they were labeled as "nonpolypoid."

All endoscopists had the credentials required to participate in the organized FIT-based screening program (more than 300 colonoscopies/year, cecal intubation rate ≥95%, adenoma detection rate ≥25%). They received formal training (a 30-minute lecture focused on the use of the CADe system and on the available evidence for the role of AI in colonoscopy) and performed at least 10 colonoscopies with CADe before entering the study.

All identified polyps were removed (nonresectable lesions were biopsied), except for diminutive (1–5 mm) polyps with clearly hyperplastic appearance located in the rectum and judged by the endoscopist as not clinically significant.

Artificial intelligence system

A dedicated CNN-based CADe system for polyp detection, CAD EYE, has been recently developed by Fujifilm Co. (Tokyo, Japan). The CAD EYE is a real-time computer-assisted image analysis system that allows automatic polyp identification without modifications to the colonoscope or to the actual endoscopic procedure. The system has been previously described in detail [13]. Briefly, when CAD EYE identifies a polyp, both a visual and an acoustic alarm pop up to attract the endoscopist’s attention. Simultaneously, around the circular edge of the endoscopic image, a light blue visual indicator (the so-called “visual assist circle”) lights up to show the direction of view of the suspected polyp, while a light blue box demarcates the polyp itself (Fig. 1). The CAD EYE system is also equipped with a characterization mode, which was not used in the current study to avoid any possible impact on study parameters, such as the inspection time.

Histopathology

All resected polyps or biopsy specimens were fixed in 10% buffered formalin solution and sent to pathology in separate jars. They were evaluated by expert pathologists (one in each center), with the credentials required to participate in the FIT-based organized CRC screening program. Participating pathologists were blinded to the assigned examination mode. All lesions were classified according to the Vienna classification [18] and World Health Organization guidelines [19]. Adenomas ≥10 mm in size and/or with significant villous features (>25%), high grade dysplasia, or early invasive cancer were defined as advanced.

Statistical analysis and sample size calculation

Age and other demographic data were presented using median and interquartile range (IQR) or frequencies. Normally distributed variables were reported with mean and SD. Comparisons of proportions were performed by two-sided chi-squared test (with Yates’ correction for continuity, if appropriate) or Fisher’s exact test, as appropriate. Relative risk (RR) along with 95% CI was also calculated. For all comparisons, a P value of ≤0.05 was be considered statistically significant. No correction for multiple testing was performed, as the analysis of the secondary outcomes, as well as subanalyses, were considered exploratory. We used a fixed analysis, without adjusting for center variability; a sensitivity analysis, which used a multilevel logistic regression model including center-specific random effects, showed virtually identical effect sizes and did not change the main analysis results (details are provided in the online-only Supplementary material).

Statistical analysis was performed using Microsoft Excel (Microsoft Co., Redmond, Washington, USA) and MedCalc Software package (MedCalc Software Ltd., Ostend, Belgium).

Several studies have shown that the ADR is higher in a FIT-based setting than in the average-risk population [20, 21]. Therefore, it has been proposed that in FIT-based screening programs the ADR recommended quality benchmark should be increased to over 50% [22, 23]. Taking into account that the baseline ADR (as defined above) of endoscopists participating in the present study was 42.8%, by using a CADe system for polyp detection, we considered a 10% absolute increase in ADR.
(ADR 53 %) as clinically relevant. To test this hypothesis with an alpha error of 0.05 and a power of 80 %, at least 790 patients overall (395 per arm) were required (Fleiss with correction for continuity; sample size calculation was performed through the website https://riskcalc.org/samplesize/). Considering a 10 % overall dropout rate, we planned to include at least 878 patients overall.

Results
Study population
Between October 2020 and June 2021, a total of 895 FIT + individuals referred for colonoscopy were considered eligible for the study. After the exclusion of 47 before randomization (reasons for exclusion before randomization and patient flow are reported in ►Fig. 2), individuals were randomized 1:1 into two groups (CADE-assisted colonoscopy 426; HDWL colonoscopy 422). A further 48 individuals (21 in the CADE-assisted colonoscopy and 27 in the HDWL colonoscopy group) were excluded from the analysis after randomization because of inadequate...
bowel preparation or incomplete colonoscopy. Finally, 800 individuals (CADe-assisted colonoscopy 405; HDWL colonoscopy 395) were included in the study analysis.

Of the included patients, 51.1% were men, the median age was 61.0 years (IQR 55–67), and 35.1% were at their first FIT round. Individuals included in the two arms were comparable with respect to demographic features (age and sex), screening history (first vs. subsequent FIT rounds), quality of bowel preparation (BBPS 6–7 vs. BBPS 8–9), and mean insertion and inspection times (Table 1). Each center and each endoscopist participating in the study evaluated a comparable number of patients with CADe-assisted or HDWL colonoscopy.

Per-patient analysis

A total of 396 patients had at least one adenoma and 138 were detected with one advanced adenoma, giving an overall ADR of 49.5% (95% CI 45.9–53.0%) and an advanced-ADR of 17.2% (95% CI 14.7–20.0%). A total of 217 patients in the CADe-assisted colonoscopy arm (217/405, 53.6%; 95% CI 48.6–58.5%) and 179 patients in the control arm (179/395, 45.3%; 95% CI 40.3–50.4%) were diagnosed with at least one adenoma. This resulted in a statistically significant difference in ADR between the two arms (RR 1.18; 95% CI 1.03–1.36). Although no significant differences at univariable analysis were observed among the two study groups as far as age and sex were concerned, patients in the CADe group were slightly older and more were male. We therefore performed an age- and sex-adjusted analysis, which confirmed that the ADR was significantly higher in the CADe group than in the HDWL group (56.1% [95% CI 50.2–61.8%] vs. 45.3% [95% CI 39.5–51.1%]; RR 1.24 [95% CI 1.05–1.45]).

The advanced-ADR was not significantly different between the two arms: 18.5% (95% CI 14.8–22.6%) in the CADe arm and 15.9% (95% CI 12.5–19.9%) in the HDWL colonoscopy arm (RR 1.18; 95% CI 0.96–1.09).

The rate of patients with at least one diminutive adenoma was higher in the study group (170/405, 41.9%; 95% CI 37.1–46.9%) than in the control group (131/395, 33.1%; 95% CI 28.5–38.0%). Similarly, a difference was observed in the rate of patients with at least one lesion with poly-poid morphology (180/405, 44.4% [95% CI 39.5–49.4%] vs. 142/395, 35.9% [95% CI 31.2–40.9%]) in the study and control arms, respectively. Conversely, no differences were found for the rate of patients with small (6–9 mm), large (≥10 mm), and nonpolyoid lesions. Furthermore, no evidence of differences across the two study groups was observed in the ADR according to polyp location (Table 2).

The detection rate of non-neoplastic lesions was 20.0% (81/405; 95% CI 16.2–24.2%) and 14.7% (58/395; 95% CI 11.3–18.6%) in the CADe-assisted and HDWL colonoscopy groups, respectively (RR 1.36; 95% CI 1.00–1.85). Furthermore, the proportion of patients with at least one SSL was comparable (RR 0.99; 95% CI 0.95–1.02) in the intervention and control arm (23/405, 5.7% [95% CI 3.6–8.4%] vs. 19/395, 4.8% [95% CI 2.9–7.4%]) (Table 1).

Subanalysis according to endoscopists’ expertise

Following stratification of endoscopists into the three predefined ADR groups, seven were included in group 1 (mean baseline ADR 36.6% [SD 3.8]), eight in group 2 (mean baseline ADR 43.7% [SD 1.5]), and six in group 3 (mean baseline ADR 49.5% [SD 2.9]). A comparable number of individuals were evaluated in all three groups (251, 293, and 256 in groups 1, 2, and 3, respectively) and according to the study arm. An absolute increase was observed with CADe assistance compared with HDWL alone for all the subgroups: group 1+7%, group 2+11%, and group 3+8%. Detailed results are reported in Table 3.

Per-polyp analysis

Overall, 1116 polyps were detected, of which 813 (72.8%; 95% CI 70.1–75.4%) were adenomas (455 in the CADe arm and 358 in the HDWL arm), 284 (25.4%; 95% CI 22.9–28.1%) were non-neoplastic lesions (165 in the CADe arm and 119 in the HDWL arm), and 19 (1.7%; 95% CI 1.0–2.6%) were not retrieved (10 in the CADe arm and 9 in the HDWL colonoscopy arm) (Table 2).

Among the 813 adenomas, 140 (17.2%; 95% CI 14.7–19.9%) had advanced histology (81 in the CADe arm and 59 in the HDWL arm), 411 (50.6%; 95% CI 47.1–54.4%) were located in the proximal colon (228 in the CADe arm and 183 in the
HDWL arm), and 146 (18.0%; 95%CI 15.4%–20.8%) had nonpolypoid morphology (71 in the CADe arm and 75 in the HDWL arm). Detailed characteristics of adenomas, according to study arm, are summarized in Table 4. Data concerning SSL features, according to study arm, are reported in Table 1.

The overall APC was 1.031 (SD 1.481). APC was significantly higher in CADe-assisted colonoscopy than in HDWL colonoscopy (1.13 [SD 1.54] vs. 0.90 [SD 1.32]) (Table 3). No statistically significant differences in APC between study and control groups were found according to polyp size and morphology (Table 3).

### Discussion

Within a FIT-based organized CRC screening program, CADe-assisted colonoscopy resulted in an absolute difference of 8.3% and 0.23 for ADR and APC, corresponding to a relative increase of 18% and 25%, respectively. The impact of the CADe system was not affected by the endoscopist’s competence as defined by the baseline ADR.

The main distinctive feature of our study is represented by the study setting. Although recent randomized trials have demonstrated the effectiveness of CADe systems in patients undergoing colonoscopy for mixed indications [8, 24], data in FIT + patients are limited by underpowered subgroup analyses [7, 11]. The population-based organized FIT-based CRC screening program is a unique setting as the population included has a high prevalence of precancerous lesions and endoscopists’ participation in the screening program is dependent on a high ADR, which is continuously monitored and audited. Interestingly, several techniques and devices aimed at increasing polyp detection that provided encouraging results in the general population, did not confirm their effectiveness when applied to a screening setting [25–27]. The results of our study confirm that in a large and homogeneous population of FIT + individuals, there was a significant absolute increase in ADR that

<table>
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<tr>
<th>Table 3</th>
<th>Adenoma detection rate in the two study arms, according to endoscopist baseline adenoma detection rate.</th>
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<tbody>
<tr>
<td></td>
<td>ADR, 95% CI</td>
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<td></td>
<td>HD-WL colonoscopy</td>
</tr>
<tr>
<td>Group 1 (ADR ≤ 40%)</td>
<td>44.4% (35.3–53.9)</td>
</tr>
<tr>
<td>Group 2 (ADR 41%–45%)</td>
<td>42.8% (34.7–51.3)</td>
</tr>
<tr>
<td>Group 3 (ADR ≥ 46%)</td>
<td>48.8% (40.0–57.7)</td>
</tr>
</tbody>
</table>

CADe, computer-aided detection; ADR, adenoma detection rate; HD-WL, high definition white light; RR, relative risk.

<table>
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<tr>
<th>Table 4</th>
<th>Features of adenomas according to study arm.</th>
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<tbody>
<tr>
<td></td>
<td>CADe-assisted colonoscopy</td>
</tr>
<tr>
<td>Adenoma features, n</td>
<td>455</td>
</tr>
<tr>
<td>Location, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Proximal</td>
<td>228 (50.1)</td>
</tr>
<tr>
<td>• Distal</td>
<td>227 (49.9)</td>
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<tr>
<td>Size, n (%)</td>
<td></td>
</tr>
<tr>
<td>• ≤ 5 mm</td>
<td>300 (65.9)</td>
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<tr>
<td>• 6–9 mm</td>
<td>76 (16.7)</td>
</tr>
<tr>
<td>• ≥ 10 mm</td>
<td>79 (17.4)</td>
</tr>
<tr>
<td>Morphology, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Polypoid</td>
<td>384 (84.4)</td>
</tr>
<tr>
<td>• Nonpolypoid</td>
<td>71 (15.6)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Low risk adenoma</td>
<td>374 (82.2)</td>
</tr>
<tr>
<td>• Advanced adenoma</td>
<td>81 (17.8)</td>
</tr>
</tbody>
</table>

CADe, computer-aided detection; HD-WL, high definition white light.
might lead to a relevant reduction of interval cancers [28]. Of note, the absolute increase was lower than the hypothesized 10% difference; nevertheless, this was mostly due to the increase in ADR in the HDWL group, when compared with the baseline figure, and the target ADR (53%) was achieved.

The relevance of ADR as a colonoscopy quality metric has been recently questioned, as it is burdened with a relevant methodological limitation [29,30], the so-called “one-and-done” effect. Notably, in organized screening programs, the number of polyps found at index colonoscopy influences the efficiency of the whole prevention process; recently updated guidelines emphasize the multiplicity issue as one of the main drivers of post-polypectomy surveillance [31]. In the present study an increase in APC was also observed. APC has been advocated as a more reliable estimate of effective mucosal exploration and it has been recently validated as a key quality measure of colonoscopy, due to its strong inverse correlation with post-colonoscopy CRC [32]. Therefore, our data support the potential clinical effectiveness of the CADe system in the FIT-based organized CRC screening program.

Unlike other tools aimed at increasing ADR (e.g. advanced imaging technologies or mucosal exposure devices), in which the contribution is mainly limited to low detectors [26,27], CADe seems to be effective in increasing adenoma detection regardless of the endoscopist’s expertise, confirming a previous observation comparing expert and nonexpert endoscopists [11]. Moreover, our data result from a comparison not based on endoscopist’s age or experience (all endoscopists were credentialed to participate in the screening program) but rather on the baseline ADR, and this represents a methodological strength of the study. Interestingly, when endoscopists were stratified into three incremental predefined baseline ADR groups, a consistent trend toward an increase in ADR was observed in each group. Despite the fact that these data need to be considered with caution, as they are derived from a subanalysis, they seem to confirm that CADe contribution is somewhat independent of the withdrawal technique, as reported in some tandem studies [33,34].

According to previous randomized controlled studies, we confirmed that the increase in ADR in the screening setting is also independent of main polyp features. This observation may be disappointing, as it would be desirable for CADe systems to aid endoscopists in recognizing difficult-to-identify lesions, such as right-sided nonpolypoid lesions. Considering these issues, it could be argued that the clinical contribution of CADe may be limited due to the potential to increase the endoscopists’ workload without any actual long-term clinical benefit. However, clinical studies targeted around ADR are not powered to detect an increase in recognition of small–large or advanced adenomas. This was the case in the present study, where a trend in a higher advanced-ADR was observed in the CADe arm, although the increase was not significantly different. In addition, although high grade dysplasia is found in less than 1% of diminutive adenomas, and their natural history is not as clearly associated with interval cancer as in the case of adenomas > 1 cm in size, diminutive polyps are still the most frequently missed polyps, even by expert endoscopists.

The main study limitation is related to practical and organizational issues. Unlike previous studies [35], in our setting it was impossible to blind the endoscopist. However, the ADR in the control arm was comparable to that measured before starting the study, thus ruling out any major bias in our study. We did not stratify patients in relation to factors that have a potential effect on polyp detection (e.g. smoking status, body mass index), but the randomized controlled design contributed to minimizing this issue. Another potential limitation is the use of a technical outcome measure, namely ADR, as the primary end point. However, the use of more clinically relevant end points, such as incidence of interval cancer or cancer-related mortality, is unfeasible in a clinical setting. Results concerning secondary outcomes must be interpreted with caution as they are exploratory analyses. Furthermore, a potential limitation of the current study was the large number of endoscopists, preventing a per-endoscopist evaluation. However, the involvement of many operators has allowed us to take a reliable picture of current clinical practice, where there is a wide variation in ADR. Moreover, stratification according to baseline ADRs is based on arbitrary threshold values; nevertheless, this policy generated three similar groups in terms of number of endoscopists, number of endoscopists per center, and number of colonoscopies per group. Finally, in the present study we did not systematically report the rate of false-positive and false-negative CADe findings. However, previous studies have demonstrated that the impact of false positives on colonoscopy duration is negligible [36,37].

In conclusion, our data confirm the usefulness of CADe systems for the detection of precancerous lesions, even in the context of FIT-based organized CRC screening programs, allowing all endoscopists to achieve higher ADR values, which is desirable in this specific subgroup of patients. These results prompt further consideration of the incorporation of CADe-assisted colonoscopy into FIT-based organized CRC screening programs.

Acknowledgments

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Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT04691401 | Type of study: Prospective, Multicentre, Randomized, Controlled Trial

Competing interests

E. Rondonotti has received speaker honoraria from Fujifilm Co., is a member of Fujifilm Co. expert group, and is a consultant for Medtronic Co. S. Paggi and A. Amato have received speaker honoraria from Fujifilm Co. F. Radaelli has received speaker honoraria and a research grant (not related to the present study) from Fujifilm Co. C. Hassan C has received equipment on loan from Fujifilm Co. A. Repici is a consultant for and has received research grants (not related to the present study) from Fujifilm Co., Medtronic plc, and Boston Scientific Co; he is also a consultant for Cosmo Pharmaceuticals S.p.A. and Erbe Elektro- medizin GmbH. The remaining authors declare that they have no conflict of interest.

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