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Role of Artificial Intelligence in Colonoscopy Detection of Advanced Neoplasias

A Randomized Trial

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Background: The role of computer-aided detection in identifying advanced colorectal neoplasia is unknown.

Objective: To evaluate the contribution of computer-aided detection to colonoscopic detection of advanced colorectal neoplasias as well as adenomas, serrated polyps, and nonpolypoid and right-sided lesions.

Design: Multicenter, parallel, randomized controlled trial. (ClinicalTrials.gov: NCT04673136)

Setting: Spanish colorectal cancer screening program.

Participants: 3213 persons with a positive fecal immunochemical test.

Intervention: Enrollees were randomly assigned to colonoscopy with or without computer-aided detection.

Measurements: Advanced colorectal neoplasia was defined as advanced adenoma and/or advanced serrated polyp.

Results: The 2 comparison groups showed no significant difference in advanced colorectal neoplasia detection rate (34.8% with intervention vs. 34.6% for controls; adjusted risk ratio [aRR], 1.01 [95% CI, 0.92 to 1.10]) or the mean number of advanced colorectal neoplasias detected per colonoscopy (0.54 [SD, 0.95] with intervention vs. 0.52 [SD, 0.95] for controls; adjusted rate ratio, 1.04 [99.9% CI, 0.88 to 1.22]). Adenoma detection rate also did not differ (64.2% with intervention vs. 62.0% for controls; aRR, 1.06 [99.9% CI, 0.91 to 1.23]). Computer-aided detection increased the mean number of nonpolypoid lesions (0.56 [SD, 1.25] vs. 0.47 [SD, 1.18] for controls; adjusted rate ratio, 1.19 [99.9% CI, 1.01 to 1.41]), proximal adenomas (0.94 [SD, 1.62] vs. 0.81 [SD, 1.52] for controls; adjusted rate ratio, 1.17 [99.9% CI, 1.03 to 1.33]), and lesions of 5 mm or smaller (polyps in general and adenomas and serrated lesions in particular) detected per colonoscopy.

Limitations: The high adenoma detection rate in the control group may limit the generalizability of the findings to endoscopists with low detection rates.

Conclusion: Computer-aided detection did not improve colonoscopic identification of advanced colorectal neoplasias.

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Colorectal cancer (CRC) screening has led to a reduction in CRC mortality rate and incidence thanks to detection and excision of premalignant lesions, such as adenomas and serrated polyps (1–5). Detection rates for adenoma and serrated polyps have been associated with postcolonoscopy CRC incidence (6–8), and improvement in these quality indicators is expected to enhance the preventative effectiveness of CRC screening. Systems relying on artificial intelligence using deep-learning technology have been linked to improved adenoma detection rates (ADRs) in different clinical settings (9–13) and also helped to reduce adenoma miss rates (14–16). A limitation, however, is that ADRs may increase due to enhanced detection of small polyps and nonadvanced adenomas, whereas improved detection of advanced and more clinically significant lesions by the artificial intelligence systems has not been established.

Fecal immunochemical test (FIT)–based CRC screening can identify people at higher risk for developing advanced colorectal neoplasias and represents the ideal setting for assessing the potential of computer-aided detection to increase identification of advanced lesions. Studies published to date have not been powered to find differences in detection rates for these advanced lesions. We designed a randomized controlled trial with the primary aim of determining whether computer-assisted colonoscopy leads to increased detection of advanced colorectal neoplasias in patients with positive FIT results in organized CRC screening programs. The secondary aims were to assess the role of computer-aided detection in identification of adenomas, serrated polyps, and nonpolypoid or right-sided lesions.

Methods

Study Design

This multicenter, parallel, controlled, randomized trial was conducted in 6 Spanish centers participating in population-based CRC screening programs. The study

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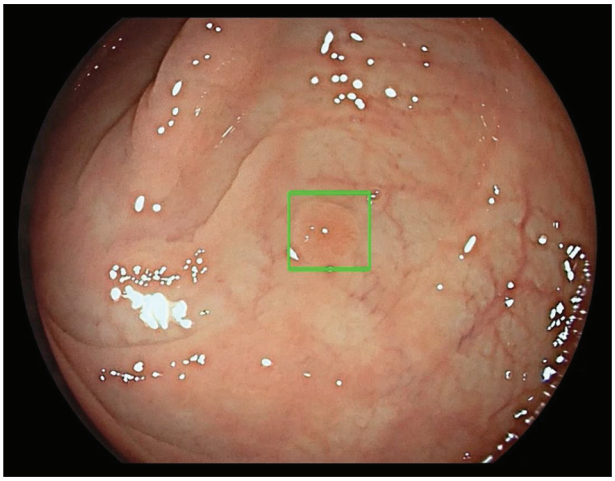
Figure 1. On polyp identification by the computer-aided detection device, a green box surrounds the lesion to allow attention of the endoscopist and real-time evaluation.



was reported according to the CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) guidelines for randomized controlled trials and registered at ClinicalTrials.gov (NCT04673136). The Institutional Review Board of Hospital General Universitario Dr. Balmis approved the protocol on 23 November 2020, and all participants gave written informed consent on the day of the procedure, once they arrived at the Endoscopy Unit. All information regarding patient demographic data, procedures, pathology reports, or physicians was registered anonymously in the REDCap (Research Electronic Data Capture) database.

Study Population

We enrolled consecutive individuals presenting for colonoscopy after a first positive FIT (cutoff hemoglobin 20 μg/g feces) on CRC screening. Individuals with complete colonoscopy with cecal intubation and adequate colon cleansing (see the **Supplement**, available at Annals.org) were included. Patients were excluded if they had a personal history of CRC, inflammatory bowel disease, colorectal surgery, terminal illness or severe disease, familial CRC or family history of inherited CRC syndrome, or lack of informed written consent.

Randomization and Intervention

Before the colonoscopy, endoscopists randomly allocated (1:1) eligible participants to receive colonoscopy with or without assistance of the computer-aided detection system during the withdrawal phase of the procedure. Randomization was based on a list of random numbers automatically generated by the coordinating center and stratified by center and enrollee sex and age. The allocation sequence was incorporated into the electronic data record dashboard (REDCap) and revealed once the endoscopist had registered baseline characteristics of the patient in the electronic data capture system and before starting the colonoscopy. Study participants were blinded to the randomization assignment. Because of intrinsic characteristics of the computer-aided system, the endoscopist could not be blinded to patient allocation.

Artificial Intelligence Device

The computer-aided detection device is a dedicated convolutional neural network system (GI-Genius, Medtronic) for polyp detection; its characteristics and development have been extensively described elsewhere (10). Briefly, on polyp detection by the GI-Genius, a visual signal in the form of a green box surrounds the lesion, attracting the attention of the endoscopist and allowing for real-time assessment (**Figure 1**). Whether or not to remove the highlighted lesion was at the discretion of the endoscopist. The version of the artificial intelligence device used in our study was 2.0.0 and remained static over the study in all participating centers. Additional information about the computer-aided device is reported in the **Supplement**.

Histopathology

In each center, pathologists who are specialists in gastrointestinal oncology evaluated polyp histology following the World Health Organization classification (17). Pathologists were blinded to patient group. All lesions were classified as adenomas (tubular, villous, or tubulovillous), serrated lesions (including hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas), or carcinomas. Advanced adenomas were defined as those with at least 1 of the following: villous component of 20% or more, size of 10 mm or greater, or high-grade dysplasia. Advanced serrated lesions were defined as being 10 mm or larger and/or with a dysplastic component or as any traditional serrated adenoma.

Definitions and Outcome Measures

The primary outcome was the advanced colorectal neoplasia detection rate, defined as the proportion of patients with at least 1 histologically proven advanced adenoma or advanced serrated lesion, or both types.

Secondary outcomes included mean number per colonoscopy of advanced colorectal neoplasias, adenomas, serrated lesions, polyps, advanced adenomas, and advanced serrated lesions. Mean values were calculated based on total number of colonoscopies performed. We also determined detection rates for adenomas (analyzed according to size: ≤5 mm, 6–9 mm, ≥10 mm), advanced adenomas, serrated lesions (also evaluated by size [≤5 mm, 6–9 mm, ≥10 mm], with exclusion of rectosigmoid hyperplastic polyps ≤5 mm), advanced serrated lesions, CRC, polyps (protuberance into the lumen above the surrounding colonic mucosa), nonpolypoid lesions (a flat or lateral spreading lesion according to the Paris classification [18]), and proximal adenomas or proximal serrated lesions, defined as proximal to the splenic flexure (including cecum and ascending and transverse colon). Detection rates were calculated as the proportion of individuals with at least 1 detected or histologically proven lesion of interest divided by the number of study participants.

Statistical Analysis

Sample Size Calculation

The baseline detection rate for advanced adenomas and advanced serrated lesions (advanced colorectal

neoplasias) in the Spanish FIT-based CRC screening program is around 35% (range, 22% to 50%) (19, 20). These data are in line with the advanced ADRs reported in other FIT-based screening programs (for example, 29% in Italy and 37.9% in the Netherlands) (21, 22). Additionally, an absolute increase of 5% in advanced colorectal neoplasia identification with computer-aided detection was considered clinically relevant. According to previous data, the sample size needed to detect an increase of this magnitude was 1471 patients in each group (intervention and control), considering a power of 80% and an alpha error of 0.05. Assuming 15% losses after recruitment, we determined that a minimum of 3384 patients would need to be initially included and allocated.

Statistical Analysis

Categorical variables are described as frequency counts and percentages, and quantitative variables are described using means and standard deviations (SDs). Two-sided *P* values of 0.05 and 0.001 were used as the thresholds for statistical significance for primary and secondary outcomes, respectively. To evaluate the effect of the computer-aided detection system on detection rates and per-colonoscopy rates, we used a log-binominal and Poisson generalized linear mixed model (GLMM) adjusted for center and patient gender and age with random intercepts to account for the clustering effect within individual endoscopists, respectively. Results are expressed using adjusted risk ratios (aRRs) and rate ratios, respectively, and their 95% CI for the primary outcome and 99.9% CI for secondary outcomes. Two sensitivity analyses were conducted and presented in supplementary material. We calculated advanced colorectal neoplasia detection rate and per-colonoscopy rate for each of the centers and for 2 categories of endoscopists. We calculated the ADRs of each of the participating endoscopists considering only standard colonoscopies performed in our study and, after calculating the median, we established 2 categories of endoscopists: low and high detectors. Statistical analysis was performed using SPSS software, version 25.0 (IBM), and R software, version 4.3.0.

Role of the Funding Source

Medtronic was not involved in the study design; the collection, analysis, or interpretation of the data; or the writing of the report. All authors had access to the study data and final responsibility for the decision to submit the manuscript for publication. The computer-aided detection devices were loaned by Medtronic.

RESULTS

Study Population and Baseline Characteristics

A total of 3399 persons were eligible for enrollment from April 2021 through March 2022. Among them, 186 patients were excluded during colonoscopy according to the predefined exclusion criteria (Figure 2). The remaining 3213 patients (1610 in the intervention group and 1603 in the control group) were included for analysis and the compliance rate to the intervention group was 100% in the study. Mean age was 61 years (SD, 6 years); 53.4% ($n = 1717$) were men; and mean bowel preparation score was 7.8 (SD, 1.3), without differences between groups (Table 1). Mean withdrawal time was longer in the intervention group when considering either all examinations (16.9 minutes [95% CI, 16.4 to 17.4] vs. 15.7 minutes for controls [95% CI, 15.2 to 16.1]) or normal colonoscopies only (10.6 minutes [95% CI, 10.0 to 11.1] vs. 9.8 minutes for controls [95% CI, 9.4 to 10.2]). Missing data accounted for less than 10% of the total number of cases in each variable; therefore, complete-case analysis was conducted.

A total of 64 endoscopists participated in the study, and the study group allocation and their ADRs are shown in Supplement Table 1 (available at Annals.org). The vast majority ($n = 48$) of the endoscopists had a balanced allocation between both study groups. Only 16 physicians with low volumes had an unbalanced allocation (Supplement Figure 1, available at Annals.org).

Advanced Colorectal Neoplasias

The groups did not differ in the primary study outcome of detection of advanced colorectal neoplasias (34.8% with intervention [95% CI, 32.5% to 37.2%] vs.

Figure 2. Study flowchart.

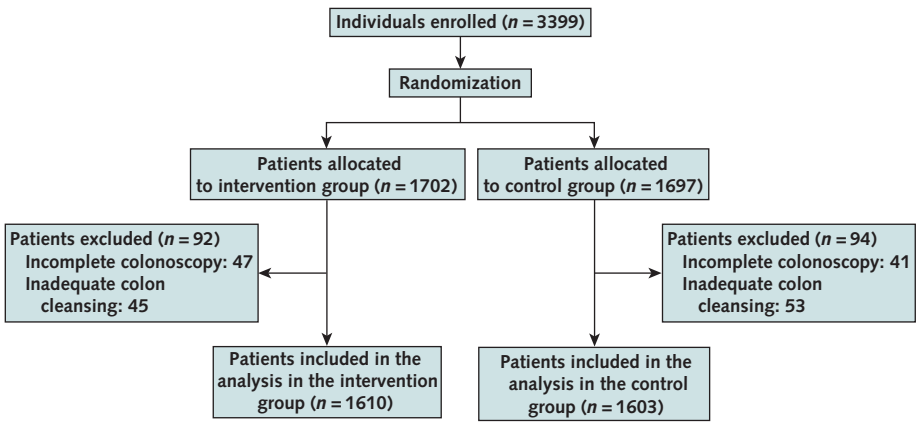


Table 1. Baseline Characteristics of Study Participants

Characteristic	Total ($n = 3213$)	Intervention Group ($n = 1610$)	Control Group ($n = 1603$)
Mean age (SD), *y*	60.7 (5.8)	60.7 (5.8)	60.6 (5.7)
Age, *n (%)*			
≥60 y	1855 (57.7)	933 (58.0)	922 (57.5)
<60 y	1358 (42.3)	677 (42.0)	681 (42.5)
Sex, *n (%)*			
Male	1717 (53.4)	865 (53.7)	852 (53.2)
Female	1496 (46.6)	745 (46.3)	751 (46.8)
Mean total bowel preparation score (SD)	7.83 (1.27)	7.84 (1.26)	7.83 (1.27)
Mean withdrawal time (SD)*, *min*	16.3 (9.9)	16.9 (10.3)	15.7 (9.4)
Mean withdrawal time in normal colonoscopies (SD)†, *min*	10.2 (4.8)	10.6 (5.3)	9.8 (4.3)

* The information was missing in 17 cases and 14 cases in the intervention and control groups, respectively.
† The information was missing in 4 cases and 1 case in the intervention and control groups, respectively.

34.6% for controls [95% CI, 32.2% to 36.9%]; aRR, 1.01 [95% CI, 0.92 to 1.10]), and the mean number of advanced colorectal neoplasias per colonoscopy was not increased either with the intervention (0.54 [SD, 0.95] vs. 0.52 [SD, 0.95] for controls; adjusted rate ratio, 1.04 [99.9% CI, 0.88 to 1.22]) (Table 2). Similar results were obtained among the sensitivity analyses conducted for centers and physician ADR categories (Supplement Tables 2 and 3, available at Annals.org).

When advanced lesions were evaluated separately as secondary outcomes, the groups did not differ in detection rates for advanced adenomas (30.5% with intervention vs. 31.3% for controls; aRR, 0.98 [99.9% CI, 0.84 to 1.14]) or advanced serrated lesions (6.5% with intervention vs. 5.3% for controls; aRR, 1.23 [99.9% CI, 0.77 to 1.97]). In addition, using computer-aided detection was not associated with increased mean number of advanced adenomas per colonoscopy (0.44 [SD, 0.82] vs. 0.44 [SD, 0.82] for controls; adjusted rate ratio, 1.00 [99.9% CI, 0.84 to 1.19]) or advanced serrated lesions detected (0.10 [SD, 0.45] vs. 0.08 [SD, 0.41] for controls; adjusted rate ratio, 1.25 [99.9% CI, 0.84 to 1.85]) (Table 2).

Polyps, Adenomas, and Serrated Lesions

Regarding additional secondary outcomes of the study, using computer-aided detection did not enhance ADR (64.2% vs. 62.0% for controls; aRR, 1.06 [99.9% CI, 0.91 to 1.23]). However, the intervention was associated with small improvements in mean number of polyps (2.54 [SD, 3.17] vs. 2.25 [SD, 3.17] for controls; adjusted rate ratio, 1.13 [99.9% CI, 1.05 to 1.22]) and adenomas detected per colonoscopy (1.78 [SD, 2.38] vs. 1.59 [SD, 2.20] for controls; adjusted rate ratio, 1.12 [99.9% CI, 1.02 to 1.22]) (Table 2).

Subanalysis of Lesions According to Morphology, Location, and Size

The intervention was associated with an increased mean number of nonpolypoid lesions detected per colonoscopy (0.56 [SD, 1.25] vs. 0.47 [SD, 1.18] for controls; adjusted rate ratio, 1.19 [99.9% CI, 1.01 to 1.41]) and an enhanced detection of nonpolypoid lesions of 10 mm or larger (6.8% with intervention vs. 5.5% for controls; aRR, 1.25 [99.9% CI, 1.24 to 1.26]). Small improvements in mean number of proximal lesions were also observed, specifically in adenomas (0.94 [SD, 1.62] vs. 0.81 [SD, 1.52] for controls; adjusted rate ratio, 1.17 [99.9% CI, 1.03 to 1.33]). Similar results were obtained in lesions of 5 mm or smaller, either polyps (1.68 [SD, 2.42] vs. 1.40 [SD, 2.25] for controls; adjusted rate ratio, 1.20 [99.9% CI, 1.09 to 1.32]), adenomas (1.12 [SD, 1.84] vs. 0.97 [SD, 1.75] for controls; adjusted rate ratio, 1.16 [99.9% CI, 1.04 to 1.30]), or serrated lesions (0.25 [SD, 0.84] vs. 0.19 [SD, 0.68] for controls; adjusted rate ratio, 1.31 [99.9% CI, 1.02 to 1.68]) (Figure 3; Supplement Tables 4 and 5, available at Annals.org).

DISCUSSION

The computer-aided detection system used in this study did not increase detection of advanced colorectal neoplasias even in the context of a high lesion prevalence and with an adequately powered study design. Contrary to previous findings (10, 11, 13, 23–25) and in line with some real-world data (26), the intervention was not associated with increased global ADRs in this context. The results seem to confirm a small increase in mean number of polyps and adenomas per colonoscopy, as previously reported in smaller studies (9–12, 24, 25). Computer-aided detection also was linked to slight increases in detection of large nonpolypoid lesions and mean numbers of nonpolypoid lesions and proximal adenomas, as well as small lesions (≤5 mm).

To date, studies evaluating colonoscopy with computer-aided detection have been inadequately powered to investigate differences in detection of advanced lesions (9–12, 24, 25), as confirmed in a meta-analysis (23). The primary aim of our study was to assess the capacity of computer-aided detection to identify advanced lesions, and for this purpose, we enrolled adequate numbers of participants to detect potential differences. Furthermore, the specific context of this study relied on a population with the highest prevalence of advanced colorectal neoplasias: FIT-positive patients in a CRC screening program, which selects for cases involving large, histologically advanced and nonpolypoid lesions. This setting offered the best context for investigating the ability of computer-aided detection to support the diagnosis of advanced colorectal neoplasias. Previous randomized controlled trials addressing this question found similar patterns to ours, with increased detection of small adenomas and hyperplastic polyps but no convincing differences in detection of

larger lesions. A meta-analysis identified a similar trend to those we identified here, with an increased mean number of adenomas per colonoscopy in all size ranges, regardless of location or shape (23). Our results are not in complete agreement with the findings of that meta-analysis, however, even with a comparable sample size. Several potential factors could explain these differences. First, as noted, our population was selected based on FIT testing and was expected to have advanced ADRs higher than those found in a symptomatic or primary screening colonoscopy population.

The detection rate in the control group was high in this study. Although all of the participating centers were tertiary hospitals, endoscopists were not selected based on quality criteria and no rules have been established for endoscopists in Spain to participate in CRC screening programs. Additionally, no imbalance was observed in the allocation distribution of study groups in terms of endoscopists. Currently, the recommended cutoff point for ADR in FIT-based colonoscopies is 40% or greater (27) and many European CRC population screening programs describe an ADR above this cutoff point (20, 28, 29). In the Spanish CRC screening program, the ADR is 58%, similar to that found in the control group of our study (19). Therefore, we consider that the results are a reflection of the usual practice of screening colonoscopies after a postive FIT finding.

Some studies have shown that use of computer-aided detection can play a prominent role in outcomes for newer endoscopists and trainees, and use of these systems likely is of great help in improving detection rates for low performers (30). The cutoff point used in the sensitivity analysis by endoscopist group in our study was somewhat high. It is possible that lower cutoff points (that is, 40%) could have shown these differences, although we could not perform these analyses due to the small number of endoscopists who would be included in the "low detector" group. Moreover, in most published randomized controlled trials, detection rates in the control groups have been low (9, 11–13, 24, 25), which would emphasize any enhanced performance associated with computer-aided detection.

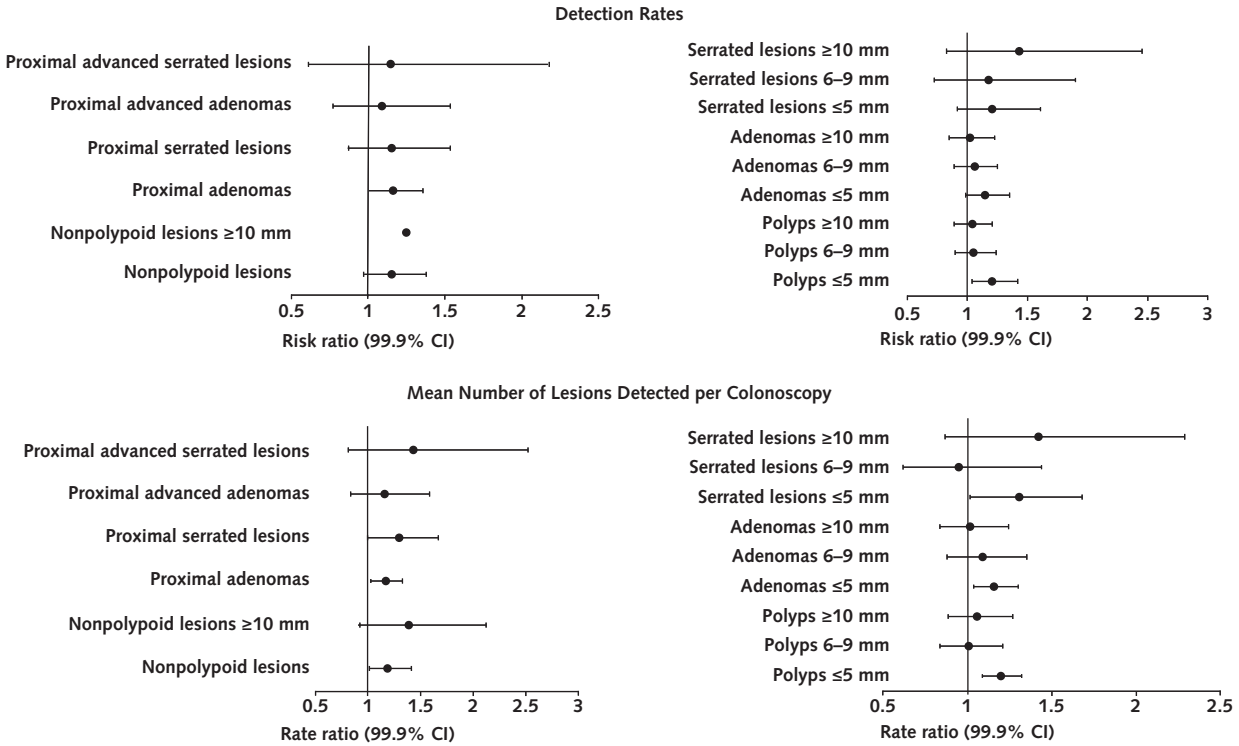
Even with the potential influences of a high-prevalence clinical population and high-performing endoscopists, we found some improvement in secondary quality indicators, although of modest magnitude and minor clinical relevance. The mean number of adenomas per colonoscopy was globally improved with the intervention, especially in adenomas of 5 mm or smaller. The same pattern held for serrated polyps, nonpolypoid lesions, and proximal adenomas. The clinical relevance of our findings centers specifically on the balance between increased detection of small adenomas but not of advanced lesions. The ADR has been identified as the most important quality indicator of a colonoscopy (31), and any improvement seen with the use of computer-aided detection or any other system is welcome. The ADR has been closely related to the diagnosis of post-colonoscopy CRC (6, 7, 32) and a higher rate of CRC at surveillance. However, a remaining question is whether increasing this detection rate or other quality indicators is associated with concordant increases in advanced lesion detection or is sufficiently important on its own. Another question is how much room for action is left to prevent CRC in these high ADR contexts when we improve detection of small lesions, considering that nonadvanced lesions have a low prevalence of cancer with a long adenoma-carcinoma sequence and, therefore, have little clinical relevance. In contrast, it is in advanced lesions where the burden of screening to prevent CRC remains, specifically in FIT-based screening,

Table 2. Detection of Colonic Lesions in the Study

Outcome	Intervention Group ($n = 1610$)	Control Group ($n = 1603$)	Risk Ratio* (99.9% CI)	Rate Ratio* (99.9% CI)	*P* Value
Primary outcome, % *(n)*					
Advanced colorectal neoplasia detection rate†	34.8 (560)	34.6 (553)	1.01 (0.92 to 1.10)	–	0.91
Secondary outcomes , % *(n)*					
Advanced adenoma detection rate†	30.5 (490)	31.3 (500)	0.98 (0.84 to 1.14)	–	0.60
Advanced serrated lesion detection rate‡	6.5 (104)	5.3 (84)	1.23 (0.77 to 1.97)	–	0.14
CRC detection rate	3.7 (59)	3.2 (51)	1.15 (0.62 to 2.13)	–	0.46
Polyp detection rate	73.4 (1182)	70.1 (1124)	1.11 (0.94 to 1.30)	–	0.036
Adenoma detection rate†	64.2 (1033)	62.0 (990)	1.06 (0.91 to 1.23)	–	0.23
Serrated lesion detection rate‡	21.3 (343)	17.1 (273)	1.21 (0.96 to 1.52)	–	0.008
Mean number of lesions detected per colonoscopy (SD)					
Advanced colorectal neoplasia†	0.54 (0.95)	0.52 (0.95)	–	1.04 (0.88 to 1.22)	0.44
Advanced adenomas†	0.44 (0.82)	0.44 (0.82)	–	1.00 (0.84 to 1.19)	0.98
Advanced serrated lesions§	0.10 (0.45)	0.08 (0.41)	–	1.25 (0.84 to 1.85)	0.063
Polyps	2.54 (3.17)	2.25 (3.17)	–	1.13 (1.05 to 1.22)	<0.001
Adenomas†	1.78 (2.38)	1.59 (2.20)	–	1.12 (1.02 to 1.22)	<0.001
Serrated lesions‡	0.38 (1.11)	0.31 (1.09)	–	1.22 (1.00 to 1.49)	0.001

CRC = colorectal cancer.
* After adjustment for center, endoscopist, and patient sex and age. The CI shown for the primary outcome is the 95% CI.
† The information was missing in 2 cases and 7 cases in the intervention and control groups, respectively.
‡ The information was missing in 2 cases and 8 cases in the intervention and control groups, respectively.
§ The information was missing in 2 cases and 9 cases in the intervention and control groups, respectively.

Figure 3. Detection rates (*top*) and mean number of lesions detected per colonoscopy (*bottom*) according to morphology, location, and size.



Results were adjusted for center, endoscopist, and patient sex and age.

with a higher sensitivity for detecting advanced adenomas (23.8%) and lower for nonadvanced adenomas (7.6%) (33).

Contrary to findings in previous publications (10, 24, 25), we did not observe an increase in ADR. As we have previously mentioned, our study was developed in a very specific context, FIT-based CRC screening, and to our knowledge only 1 previous study has been conducted in this scenario (24). One of the possible reasons why we have not found differences is the higher rate of ADR that we found in the control group compared to that reflected in the Italian study (62.0% vs. 45.3%). Additionally, withdrawal time was longer in both groups with respect to withdrawal time reported in other clinical trials (9–12, 24, 25), and this might reflect greater attention and thoroughness on the part of the endoscopists in our study. Probably this high rate in the control group leaves little room for artificial intelligence devices to improve lesion detection. It is possible that in contexts of lower ADR or in groups of endoscopists considered as "low detectors" there may be more effect of computer-aided detection systems.

The current findings are a snapshot of what these systems can currently offer and what can be expected from them. Detecting more advanced lesions still lies in the hands of experienced endoscopists who can recognize the lesions and achieve adequate mucosal exposure. Some studies have found an improvement in identification of subtle lesions using computer-aided detection, especially for laterally spreading and flat lesions (34). This capacity is especially relevant for the diagnosis of large nonpolypoid lesions, which were increased in our study in the intervention group. However, our results show the field has room for improvement. The findings emphasize the need to train new versions of deep-learning models with larger data sets of advanced nonpolypoid lesions to improve their capacity to locate these frequently difficult-to-detect lesions that potentially are the primary source of colonoscopy miss rates (35). Artificial intelligence also has other important quality-improvement roles in colonoscopy, such as optical diagnosis, quality assurance, better mucosal exposure, or higher homogeneity of cecal intubation or colonic cleansing evaluation.

Some strengths of this study are its large sample size and homogeneous setting of FIT-based CRC screening with a high rate of advanced and nonadvanced colorectal neoplasias. Further strengths are the multicenter setting with many nonselected endoscopists, which adds value for the generalization of our results. Our study also has some limitations. The high detection rate in the control group made it untenable to evaluate the role of computer-aided detection used by trainees or endoscopists with low detection rates. Although information about false-positive and false-negative rates could be relevant for evaluating the effectiveness of computer-aided detection systems, we could not collect these data in our study. While the type I error was adjusted for multiple testing for the between-group comparisons of secondary outcomes,

these secondary findings should be interpreted with caution.

In summary, we found that colonoscopy assisted by computer-aided detection was not associated with improved detection of advanced colorectal neoplasias. Small effects were observed, with improved detection of large nonpolypoid lesions and increased numbers of nonpolypoid lesions, proximal adenomas, and small lesions of 5 mm or less (colonic polyps in general and adenomas and serrated polyps in particular) detected per colonoscopy. Artificial intelligence applications are in a dynamic phase. Our results show the need for improvement in this technology, using larger and more variable data sets to train deep-learning systems, and for further evaluations of these new systems in large, adequately powered randomized controlled trials.

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References

1. **Atkin WS, Edwards R, Kralj-Hans I, et al.; UK Flexible Sigmoidoscopy Trial Investigators.** Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624-1633. [PMID: 20430429] doi:10.1016/S0140-6736(10)60551-X

2. **Grobbee EJ, Wisse PH, Schreuders EH, et al.** Guaiac-based faecal occult blood tests versus faecal immunochemical tests for colorectal cancer screening in average-risk individuals. Cochrane Database Syst Rev. 2022;6:CD009276. [PMID: 35665911] doi:10.1002/14651858.CD009276.pub2

3. **Guo F, Chen C, Holleczek B, et al.** Strong reduction of colorectal cancer incidence and mortality after screening colonoscopy: prospective cohort study from Germany. Am J Gastroenterol. 2021;116:967-975. [PMID: 33929378] doi:10.14309/ajg.0000000000001146

4. **Nishihara R, Wu K, Lochhead P, et al.** Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369:1095-1105. [PMID: 24047059] doi:10.1056/NEJMoa1301969

5. **Shaukat A, Mongin SJ, Geisser MS, et al.** Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369:1106-1114. [PMID: 24047060] doi:10.1056/NEJMoa1300720

6. **Corley DA, Jensen CD, Marks AR, et al.** Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370:1298-1306. [PMID: 24693890] doi:10.1056/NEJMoa1309086

7. **Kaminski MF, Regula J, Kraszewska E, et al.** Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010;362:1795-1803. [PMID: 20463339] doi:10.1056/NEJMoa0907667

8. **van Toledo DEFWM, IJspeert JEG, Bossuyt PMM, et al.** Serrated polyp detection and risk of interval post-colonoscopy colorectal cancer: a population-based study. Lancet Gastroenterol Hepatol. 2022;7:747-754. [PMID: 35550250] doi:10.1016/S2468-1253(22)00090-5

9. **Gong D, Wu L, Zhang J, et al.** Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. Lancet Gastroenterol Hepatol. 2020;5:352-361. [PMID: 31981518] doi:10.1016/S2468-1253(19)30413-3

10. **Repici A, Badalamenti M, Maselli R, et al.** Efficacy of real-time computer-aided detection of colorectal neoplasia in a randomized trial. Gastroenterology. 2020;159:512-520 e7. [PMID: 32371116] doi:10.1053/j.gastro.2020.04.062

11. **Su JR, Li Z, Shao XJ, et al.** Impact of a real-time automatic quality control system on colorectal polyp and adenoma detection: a prospective randomized controlled study (with videos). Gastrointest Endosc. 2020;91:415-424 e4. [PMID: 31454493] doi:10.1016/j.gie.2019.08.026

12. **Wang P, Berzin TM, Glissen Brown JR, et al.** Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. Gut. 2019;68:1813-1819. [PMID: 30814121] doi:10.1136/gutjnl-2018-317500

13. **Wang P, Liu X, Berzin TM, et al.** Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. Lancet Gastroenterol Hepatol. 2020;5:343-351. [PMID: 31981517] doi:10.1016/S2468-1253(19)30411-X

14. **Hassan C, Senore C, Manes G, et al.** Diagnostic yield and miss rate of EndoRings in an organized colorectal cancer screening program: the SMART (Study Methodology for ADR-Related Technology) trial. Gastrointest Endosc. 2019;89:583-590.e1. [PMID: 30365984] doi:10.1016/j.gie.2018.10.019

15. **Glissen Brown JR, Mansour NM, Wang P, et al.** Deep learning computer-aided polyp detection reduces adenoma miss rate: a United States multi-center randomized tandem colonoscopy study (CADeT-CS Trial). Clin Gastroenterol Hepatol. 2022;20:1499-1507.e4. [PMID: 34530161] doi:10.1016/j.cgh.2021.09.009

16. **Kamba S, Tamai N, Saitoh I, et al.** Reducing adenoma miss rate of colonoscopy assisted by artificial intelligence: a multicenter

randomized controlled trial. J Gastroenterol. 2021;56:746-757. [PMID: 34218329] doi:10.1007/s00535-021-01808-w
17. **Nagtegaal ID, Odze RD, Klimstra D, et al.; WHO Classification of Tumours Editorial Board.** The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182-188. [PMID: 31433515] doi:10.1111/his.13975
18. **Endoscopic Classification Review Group.** Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy. 2005;37:570-578. [PMID: 15933932] doi:10.1055/s-2005-861352
19. **Medina-Prado L, Mangas-Sanjuan C, Baile-Maxía S, et al.** Risk of colorectal cancer and advanced polyps one year after excision of high-risk adenomas. Dis Colon Rectum. 2022;65:1112-1120. [PMID: 34840293] doi:10.1097/DCR.0000000000002068
20. **Red de Programas de Cribado de Cancer**. Situación. Datos e indicadores. Programas poblacionales de cribado de cáncer colorrectal. Accessed at https://cribadocancer.es/indicadores-cancer-colorrectal/ on 28 July 2023.
21. **Zorzi M, Senore C, Da Re F, et al; Equipe Working Group.** Quality of colonoscopy in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). Gut. 2015;64:1389-1396. [PMID: 25227521] doi:10.1136/gutjnl-2014-307954
22. **Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al; Dutch National Colorectal Cancer Screening Working Group.** Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. Gastroenterology. 2017;152:767-775.e2. [PMID: 27890769] doi:10.1053/j.gastro.2016.11.022
23. **Hassan C, Spadaccini M, Iannone A, et al.** Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. Gastrointest Endosc. 2021;93:77-85 e6. [PMID: 32598963] doi:10.1016/j.gie.2020.06.059
24. **Rondonotti E, Di Paolo D, Rosa Rizzotto E, et al.** Efficacy of a computer aided detection system in a FIT-based organized colorectal cancer screening program: a randomized controlled trial (AIFIT study). Endoscopy. 2022;54:1171-1179. [PMID: 35545122] doi:10.1055/a-1849-6878
25. **Xu H, Tang RSY, Lam TYT, et al.** Artificial intelligence-assisted colonoscopy for colorectal cancer screening: a multicenter randomized controlled trial. Clin Gastroenterol Hepatol. 2023;21:337-346.e3. [PMID: 35863686] doi:10.1016/j.cgh.2022.07.006
26. **Levy I, Bruckmayer L, Klang E, et al.** Artificial intelligence-aided colonoscopy does not increase adenoma detection rate in routine clinical practice. Am J Gastroenterol. 2022;117:1871-1873. [PMID: 36001408] doi:10.14309/ajg.0000000000001970
27. **Robertson DJ, Lee JK, Boland CR, et al.** Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017;152:1217-1237.e3. [PMID: 27769517] doi:10.1053/j.gastro.2016.08.053
28. **Wisse PHA, Erler NS, de Boer SY, et al.** Adenoma detection rate and risk for interval postcolonoscopy colorectal cancer in fecal immunochemical test-based screening: a population-based cohort study. Ann Intern Med. 2022;175:1366-1373. [PMID: 36162114] doi:10.7326/M22-0301
29. **Denis B, Sauleau EA, Gendre I, et al.** The mean number of adenomas per procedure should become the gold standard to measure the neoplasia yield of colonoscopy: a population-based cohort study. Dig Liver Dis. 2014;46:176-181. [PMID: 24054769] doi:10.1016/j.dld.2013.08.129
30. **Biscaglia G, Cocomazzi F, Gentile M, et al.** Real-time, computer-aided, detection-assisted colonoscopy eliminates differences in adenoma detection rate between trainee and experienced endoscopists. Endosc Int Open. 2022;10:E616-E621. [PMID: 35571479] doi:10.1055/a-1783-9678
31. **Kaminski MF, Thomas-Gibson S, Bugajski M, et al.** Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. Endoscopy. 2017;49:378-397. [PMID: 28268235] doi:10.1055/s-0043-103411
32. **Wieszczy P, Waldmann E, Loberg M, et al.** Colonoscopist performance and colorectal cancer risk after adenoma removal to stratify surveillance: two nationwide observational studies. Gastroenterology. 2021;160:1067-1074 e6. [PMID: 33065063] doi:10.1053/j.gastro.2020.10.009
33. **Lee JK, Liles EG, Bent S, et al.** Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160:171. [PMID: 24658694] doi:10.7326/M13-1484
34. **Hassan C, Bhandari P, Antonelli G, et al.** Artificial intelligence for non-polypoid colorectal neoplasms. Dig Endosc. 2021;33:285-289. [PMID: 32767704] doi:10.1111/den.13807
35. **McGill SK, Soetikno R, Rouse RV, et al.** Patients with nonpolypoid (flat and depressed) colorectal neoplasms at increased risk for advanced neoplasias, compared with patients with polypoid neoplasms. Clin Gastroenterol Hepatol. 2017;15:249-256.e1. [PMID: 27639328] doi:10.1016/j.cgh.2016.08.045

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