



## Lower Adenoma Miss Rate of Computer-aided Detection-Assisted Colonoscopy vs Routine White-Light Colonoscopy in a Prospective Tandem Study

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**Title:** Lower Adenoma Miss Rate of Computer-aided Detection-Assisted Colonoscopy vs Routine White-Light Colonoscopy in a Prospective Tandem Study

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**Abbreviations:** ADR, adenoma detection rate; AMR, adenoma miss rate; BBPS, Boston bowel preparation scale; BMI, body mass index; CAD, computer aided diagnosis; CADe, computer aided detection; CRC, colorectal cancer; FC, fold change; GI, gastrointestinal; IBD, inflammatory bowel disease; IRB, institutional review board; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PMR, polyp miss rate; SSA/P, sessile serrated adenoma/polyp

**Disclosure:** The CADe system (EndoScreener) was developed by Shanghai Wision AI Co., Ltd. The system was provided free-of-charge for the purpose of this study. Employees in the company were not involved in the clinical trial in any way, including in study design, statistical analysis or manuscript writing.

**Author contributions:** Pu Wang, Xun Xiao, Guanyu Zhou, Peixi Liu, Jeremy Glissen Brown and Tyler Berzin contributed to study concept and design. Liangping Li, Peixi Liu, Pu Wang, Guanyu Zhou, Xiaogang Liu contributed to acquisition of data. Pu Wang, Jeremy Glissen Brown and Tyler Berzin contributed to interpretation of data and drafting of the manuscript.

All authors read and approved the final manuscript.

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**Abstract:**

**Background & Aims:** Up to 30% of adenomas might be missed during screening colonoscopy—these could be polyps that appear on-screen but are not recognized by endoscopists or polyps that are in locations that do not appear on the screen at all. Computer-aided detection (CADe) systems, based on deep learning, might reduce rates of missed adenomas by displaying visual alerts that identify precancerous polyps on the endoscopy monitor in real time. We compared adenoma miss rates of CADe colonoscopy vs routine white-light colonoscopy.

**Methods:** We performed a prospective study of patients, 18–75 years old, referred for diagnostic, screening, or surveillance colonoscopies at a single endoscopy center of Sichuan Provincial People's Hospital from June 3, 2019 through September 24, 2019. Same day, tandem colonoscopies were performed for each participant by the same endoscopist. Patients were randomly assigned to groups that received either CADe colonoscopy (n=184) or routine colonoscopy (n=185) first, followed immediately by the other procedure. Endoscopists were blinded to the group each patient was assigned to until immediately before the start of each colonoscopy. Polyps that were missed by the CADe system but detected by endoscopists were classified as missed polyps. False polyps were those continuously traced by the CADe system but then determined not to be polyps by the endoscopists. The primary endpoint was adenoma miss rate, which was defined as the number of adenomas detected in the second-pass colonoscopy divided by the total number of adenomas detected in both passes.

**Results:** The adenoma miss rate was significantly lower with CADe colonoscopy (13.89%; 95% CI, 8.24%–19.54%) than with routine colonoscopy (40.00%; 95% CI, 31.23%–48.77%,  $P<.0001$ ). The polyp miss rate significantly lower with CADe colonoscopy (12.98%; 95% CI, 9.08%–16.88%) than with routine colonoscopy (45.90%; 95% CI, 39.65%–52.15%) ( $P<.0001$ ). Adenoma miss rates in ascending, transverse, and descending colon were significantly lower with CADe colonoscopy than with routine colonoscopy (ascending colon 6.67% vs 39.13%;  $P=.0095$ ; transverse colon 16.33% vs 45.16%;  $P=.0065$ ; and descending colon 12.50% vs 40.91%,  $P=.0364$ ).

**Conclusions:** CADe colonoscopy reduced the overall miss rate of adenomas by endoscopists using white-light endoscopy. Routine use of CADe might reduce the incidence of interval colon cancers. [chictr.org.cn](http://chictr.org.cn) study no: ChiCTR1900023086

**KEY WORDS:** Artificial intelligence, AMR, neoplasm, early detection

## Introduction

Adenomas are routinely missed during colonoscopy by individual endoscopists<sup>1</sup>. Although colonoscopy remains the gold standard for screening cancer and precancerous lesions in the colon<sup>2</sup> colonoscopy can be technically demanding as it requires both manipulation and observation at the same time, and there is significant variation in how colonoscopy is performed and how lesions are detected between individual endoscopists.

Non-visualization is a major cause of missed diagnosis, as lesions may remain hidden behind folds or debris during colonoscopy. Such lesions could be better exposed by means of high-quality bowel cleansing, endoscopic cameras with wider viewing angles, and meticulous mucosal inspection techniques<sup>1</sup>. However, adenoma miss rate (AMR) still ranges from 6% to 41% using white light colonoscopy<sup>1-3</sup>. Studies using full spectrum colonoscopy (FUSE), which provides 330° angle of view, show an adenoma miss rate between 7.0%<sup>4</sup> and 20.5%<sup>3</sup>. This indicates that lesions within the visual field may still be missed due to failure of identification by human eye.

For those polyps that are technically in the visual field, such lesions may be non-obvious, briefly visible, partially obscured or appear on the edge of the screen<sup>5</sup>. Second observer strategies that utilize either nurse observers or trainees during colonoscopy may increase polyp detection rate (PDR), but use of a second observer may or may not increase adenoma detection rate (ADR)<sup>5-9</sup>. In addition, it is likely that adding additional human observers may not completely overcome the deficiencies of human attention and human visualization in the identification of subtle colonic lesions<sup>5-9</sup>. Thanks to the breakthrough of artificial intelligence<sup>10-11</sup>, computer-aided detection (CADe) systems have been developed that show high accuracy, fidelity and consistency and in prospective randomized trials have shown promise as a standardized second observer. Such a system may help to avoid missed diagnoses for any visible lesions that appear ever briefly in the visual field by providing real-time visual alerts during colonoscopy<sup>12</sup>. The positive impact of CADe on ADR has been demonstrated prospectively in the clinical setting<sup>5-13</sup>.

While, past prospective studies have shown a clear increase in ADR, relatively little is known in regards to the exact contribution of the CADe system to the increase in detection rate. In addition, AMR, another important indicator that reflect the quality of colonoscopy, has not been specifically examined. Such a variable can directly reflect the impact of CADe by using a back-to-back comparison<sup>4</sup>. Therefore, we aim to investigate the impact of CADe on AMR by means of a tandem study. Furthermore, by comparing video records of first and second pass, the direct contribution of the CADe system may be better demonstrated.

## Methods

### Study design and patients

This study was a single-center, open labeled, prospective, randomized, tandem study, which was conducted in the endoscopy center in Caotang branch hospital of Sichuan provincial people's hospital, China between June 3, 2019 to September 24, 2019. We recruited patients from 18-75 years who had

been referred for diagnostic, screening colonoscopy or surveillance colonoscopy (for patients who underwent previous polypectomy). We excluded patients with a history of IBD, CRC, colorectal surgery, or contraindication for biopsy. Patients whom the cecum were not reached and were high suspicion for polyposis syndromes, IBD and CRC were also excluded. In addition, we excluded cases of 'difficult insertion' (defined as insertion time > 7 minutes in first pass), because of safety considerations for an already prolonged tandem procedure. Written informed consent was obtained from all participants before the colonoscopy examination.

The protocol was approved by the Institutional Review Board of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital.

### **Randomization and masking**

All eligible patients were randomized via computer-generated stratified randomization to either CAdE colonoscopy or routine colonoscopy, followed immediately by the other procedure. Block randomization with a block size of 4 was used to determine the assignment (1:1) of each participant. The randomization was performed using a digital random number generator before the procedure to either CAdE white light colonoscopy first versus routine white light colonoscopy first. Patients were blinded to the grouping. Operating endoscopists were told the group allocation by a research assistant before the start of colonoscopy procedure.

### **Interventions**

The CAdE system (EndoScreener, Shanghai Wision AI Co., Ltd. China) is a real-time automatic polyp detection system (Figure S1) developed on a deep learning architecture. In a preliminary study, the system was validated to have a per-image sensitivity of 94.38%, per-image specificity of 95.92% and an area under the receiver operating characteristic curve of 0.984 to detect colon polyps in colonoscopy report images. In addition, the system was also validated to have a per-polyp sensitivity of 100.00% (per-image sensitivity of 91.64%) and a per-image specificity of 95.40% in real-world colonoscopy videos<sup>12</sup>. The system processes >30 frames per second with a latency of  $46.56 \pm 2.79$ ms on Ge-Force-1080ti (Nvidia, CA), an imperceptible latency<sup>14</sup> for most human endoscopists. The CAdE system was integrated into the endoscopy model by means of synchronously capturing and analyzing the video stream from the endoscopy processor and displaying alert boxes directly into the primary endoscopy monitor. This CAdE colonoscopy works in an augmented reality way to assist endoscopists to detect polyps<sup>1</sup>. (video S1)

### **Procedures**

A same-day back-to-back tandem colonoscopy was performed for each eligible patient by the same endoscopist to assess AMR. All polyps were biopsied or removed by cold forceps biopsy once verified by the operating endoscopist. Larger polyps identified during colonoscopy are biopsied and referred for later complete resection, as is typical of the endoscopy workflow for a large referral center in China.

Diminutive ( $\leq 2$  mm) rectal polyps deemed by the endoscopist to be hyperplastic in nature<sup>4</sup> by use of blue laser imaging (BLI) or Fuji Intelligent Chromoendoscopy (FICE) mode according to type 1 of NBI International Colorectal Endoscopic (NICE) Classification<sup>15</sup>, were not biopsied. The location, size and morphological features according to the Paris classification of each detected polyp were recorded by the research assistant.

Colonoscopies were performed with latest-generation model (Fujifilm LASEREO and VP4450HD), high definition colonoscopes (EC-L590, EC-580, EC-590) (Fujifilm, Tokyo, Japan) and high-definition monitors. All colonoscopy exams were done with white light only, except for NICE classification for an identified polyp when BLI or FICE mode was used in a short-interval at the discretion of the colonoscopists. Anesthesia, including midazolam, fentanyl or propofol, was delivered and supervised by an anesthesiologist during colonoscopy examination for each participant. Bowel preparation method was 2 L of polyethylene glycol with 6 ml simethicone solution, given in split doses.

Three experienced endoscopists from the division of gastroenterology participated as colonoscopy performers in this study.

In the routine pass, a routine white light colonoscopy was performed. In the CAdE pass, the CAdE system processed each frame of the video stream synchronously and reported the detected polyp location with a hollow blue alert box directly in the endoscopy monitor with a simultaneous sound alarm (Video S2). The system was activated during withdrawal only. For any area alerted by the CAdE system, the endoscopist was required to check and verify the area within the box based on his or her own clinical judgement.

All polyps detected during first-pass colonoscopy were biopsied or removed using cold forceps biopsy. During the second-pass colonoscopy, any additional polyps detected were also biopsied or removed by cold forceps biopsy. The residue of polyp which was biopsied during the first pass was a mark that demonstrated the polyp had been identified during the first pass, and these lesions were not counted as detected during the second pass. Repeat biopsies of already-biopsied lesions were not taken during the second pass. All biopsied tissue was sent for pathological examination.

We measured the level of bowel cleanliness during colonoscopy with the Boston Bowel Preparation Scale (BBPS). Insertion time to the cecum, withdrawal time for each pass, and biopsy time for each lesion were all recorded with a stopwatch during each colonoscopy procedure by a staff assistant. The endoscopist estimated polyp size with an open biopsy forceps.

In the CAdE colonoscopy pass, missed polyps by the CAdE system and consistent false detections by the CAdE system were recorded. A missed polyp by the CAdE system was defined as a polyp verified by the endoscopist but undetected by the system. A consistent false detection by the CAdE system was defined as a detected area, which was continuously tracked by the system, but deemed by the endoscopist not to be a polyp. Any complication during the procedure or recovery was also recorded. All authors had access to the study data and reviewed and approved the final manuscript.

## Outcomes

The primary outcome was adenoma miss rate (AMR), which was defined as the number of

adenomas detected in the second-pass colonoscopy divided by the total number of adenomas detected in both passes. The secondary outcomes were polyp miss rate (PMR), which was defined as the number of polyps detected in the second-pass colonoscopy divided by the total number of polyps detected in both passes, in which the non-biopsied hyperplastic polyps in rectum were included. Miss rate of advanced adenomas, and SSA/Ps were calculated with the same definitions as AMR and PMR. Patient miss rate, which was defined as number of patients in whom adenomas were detected in second pass for the first time divided by the total number of patients with at least one adenoma detected. Adenoma detection rate (ADR) for the first pass was defined as the proportion of individuals with at least one adenoma detected in the first pass procedure. Adenoma per colonoscopy (APC) or polyp per colonoscopy (PPC) was defined as the total number of adenomas or polyps divided by the total number of patients of each group. We defined advanced adenomas as any adenoma of 10 mm or greater in size, or containing villous histology, or with high-grade dysplasia<sup>16 17</sup>.

Additionally, since the CAdE system is felt to help with missed polyps that appear in the visual field but remain unrecognized,<sup>1</sup> but not those that fail to appear in the visual field, to further scrutinize the contribution of the CAdE system, 3 senior expert endoscopists reviewed all video records and excluded polyps which did not appear in the visual field during the first pass. Here we define visible adenoma miss rate (AMR-V) and visible polyp miss rate (PMR-V) as the proportion of missed adenomas or polyps among all detected adenomas or polyps which were visible in first pass. Meanwhile, we define invisible adenoma miss rate (AMR-INV) and invisible polyp miss rate (PMR-INV) as the proportion of missed adenomas or polyps among all detected adenomas or polyps which were invisible in first pass.

### Statistical analysis

We prospectively designed this study to allow for 80% power or more to detect a 15% difference (30% vs 15%) in adenoma miss rates, per lesion analysis, between colonoscopy procedures with a two group  $\chi^2$  test with a two-sided  $\alpha$  level of 0.05. Thus, the overall participant enrolment goal was 392 to allow for potential exclusions or dropouts of 10%, with each participant undergoing same day, back-to-back colonoscopy (784 tandem colonoscopies in total). Descriptive statistics were calculated for all measured variables and derived parameters. For continuous variables, time to reach the caecum, colonoscope withdrawal time, and total procedure time, we calculated means, medians, IQRs, SDs, and minimums and maximums. For categorical variables, summary statistics were counts and percentages. We used t tests to compare continuous variables. For categorical variables, we used Fisher's exact test or  $\chi^2$  test to compare detection rates between groups. For estimates of proportions, we calculated 95% exact binomial CIs. All tests applied were two-tailed. We analyzed data with R (version 3.4.4).

### Role of the funding source

The study had no funding source. P W, G Z, P L and X X had full access to the raw data and had final responsibility for the decision to submit for publication.

### Results

**Baseline and demographic data (Table 1)**

A total of 386 patients were enrolled in this study, 4 patients withdrew the consent before grouping. 382 patients were randomized into the routine-first (n=190) group or CAdE first group (n=192). 13 patients were excluded during colonoscopy due to exclusion criteria. A total of 369 eligible patients were analyzed, with 185 patients in routine-first group and 184 in the CAdE first group (Figure 1). The total withdrawal time of routine-first and CAdE first groups were 7.14 minutes vs. 7.85 minutes ( $p=0.001$ ) in the first pass and 6.73 minutes vs. 6.34 minutes ( $p=0.001$ ) in the second pass respectively, possibly due to more polyps detected and more biopsy procedures performed in the CAdE colonoscopy. However, when biopsy time was excluded from analysis, the clean withdrawal time was 6.51 minutes versus 6.55 minutes ( $p=0.745$ ) in the first pass and 6.04 minutes vs. 6.14 minutes ( $p=0.146$ ) in the second pass respectively (Table S1).

There were no statistically significant differences between the two groups in demographic data, insertion time, bowel preparation level, indication for colonoscopy (Table 1) and adenoma risk factors (Table S2). No complications were reported.

**Miss rate of polyps, adenomas, advanced adenomas and SSA/P (Table 2)**

Table 2 shows the miss rate of polyps, adenomas and major polyp subtypes. The AMR was significantly lower with CAdE colonoscopy than with routine white light colonoscopy (13.89% vs. 40.00%,  $P<0.0001$ ). The PMR was also lower with CAdE colonoscopy than with routine white light colonoscopy (12.98% vs. 45.90%,  $P<0.0001$ ). There were no statistical differences in miss rate of advanced adenomas and SSA/Ps.

Table 3 shows the clinicopathologic characteristics of the missed adenomas in routine white light colonoscopy and CAdE colonoscopy. The AMR for diminutive ( $<5\text{mm}$ ) were significantly lower with CAdE colonoscopy than with routine white light colonoscopy (13.11% vs. 39.66%,  $P=0.0015$ ), as well as for small (5-9mm) adenomas (13.75% vs. 46.94%,  $P<0.0001$ ). Regarding morphology, AMR was significantly lower with CAdE colonoscopy than with routine white light colonoscopy in non-pedunculated types (14.18% vs. 42.45%,  $P<0.0001$ ). AMR was found to be lower with CAdE colonoscopy than with routine white light colonoscopy in the ascending, transverse and descending colon (Table 3).

**Miss rate of visible adenomas and polyps (Table 4)**

AMR-V was 24.21% vs. 1.59% ( $p<0.001$ ) in routine-CAdE group and CAdE-routine group, the PMR-V was 30.89% vs. 2.36% ( $p<0.001$ ) in routine-CAdE group and CAdE-routine group.

Out of 23 missed visible adenomas and 59 polyps during first pass, there were 10 (10/23, 43.48%) adenomas, and 22 (22/59, 37.29%) polyps recorded in video files being detected by CAdE system in post-hoc video analysis.

**Miss rate of invisible adenomas and polyps (Table 4)**

AMR-INV was 27.07% vs. 11.11% ( $p<0.001$ ) in routine-CAdE group and CAdE-routine group, the PMR-INV was 25.00% vs. 12.68% ( $p=0.016$ ) in routine-CAdE group and CAdE-routine group.

### ADR PDR APC and PPC (Table 5)

The overall ADR (42.39% vs. 35.68%,  $P=0.186$ ), overall PDR (63.59% vs. 55.14%,  $P=0.099$ ), overall APC (0.78 vs. 0.65,  $P=0.129$ ), and overall PPC (1.55 vs. 1.32,  $P=0.065$ ) were different between the CADe colonoscopy first group and routine colonoscopy first groups. For the first pass, there was no statistical difference found in ADR in the first pass (34.78% vs. 26.49%,  $P=0.085$ ) in CADe colonoscopy and routine white light colonoscopy, though the trend was towards a higher ADR in the CADe first group. The PDR, APC and PPC were significantly higher in CADe colonoscopy than routine white light colonoscopy, i.e. PDR for first pass was 55.98% vs. 37.84%,  $P=0.001$ . APC for first pass was 0.67 vs. 0.39,  $P<0.001$ . PPC for first pass was 1.35 vs. 0.71,  $P<0.001$ . Similar findings were found when analyzing the second pass, all ADR, PDR and APC and PPC were significantly higher in CADe colonoscopy than routine white light colonoscopy, i.e. ADR for second pass was 18.38% vs. 10.87%,  $P=0.043$ , PDR for second pass was 37.84% vs. 19.02%,  $P<0.001$ . APC for second pass was 0.26 vs. 0.11,  $P=0.001$ . PPC for second pass was 0.61 vs. 0.20,  $P<0.001$ .

### Patients miss rate (Table 6)

Patient miss rate was lower with CADe colonoscopy than with routine white light colonoscopy, but without a statistically significant difference (17.95% vs. 25.76%,  $P=0.258$ ).

### Consistent false detections with the CADe system (Table S3)

There was a total of 67 consistent false detections in the CADe colonoscopy. Most consistent false detections were wrinkled mucosa.

None was missed by the CADe system among all detected polyps by the endoscopists in the CADe colonoscopy.

### Discussion

In this single center, open-labeled tandem study, we found AMR and PMR to be significantly lower with CADe colonoscopy than routine colonoscopy. AMR obtained from tandem colonoscopy, is a more representative parameter to reflect the performance of an individual endoscopist with and without CADe than ADR. In previous tandem studies utilizing traditional colonoscopes, the reported AMR for a single standard colonoscopy has been estimated to be between 10% to 30%<sup>18 19 20 21</sup>. However, if a wide-viewing angle colonoscope is used for the second pass, AMR may be as high as 31%<sup>3</sup> to 41%<sup>4</sup>. This high miss rate is thought to translate into a higher risk of developing interval cancers for patients who undergo routine colonoscopy. By enlarging the visual field, using technology such as FUSE colonoscopy, AMR may be reduced to 7% to 20%<sup>3 4</sup>. Nevertheless, subtle polyps on the endoscopy screen can still be missed by the endoscopist, which is self-evident by the non-zero miss rate of the wide viewing angle colonoscopies and similar devices<sup>22 23 24 25 26</sup>. Furthermore, it can be challenging for an endoscopist to be fully vigilant to every section of the monitors in a multi-screen setting in colonoscopy<sup>27 28</sup>. In addition, visual gaze patterns (VGP), differ between endoscopists and it has been shown that endoscopists either with a wider VGP or center-looking VGP may have a higher adenoma or polyp detection rate than endoscopists with other VGPs<sup>29 30</sup>. Finally, “inattentional blindness”<sup>31 32</sup> and “change blindness”<sup>33</sup> phenomena may add to intra-proceduralist variability, and neither

wider-viewing colonoscopes nor second observer strategies may completely address these issues. Therefore, high-performance CAdE may serve as a more standardized “second eye” in assisting the endoscopist to avoid missing any lesion.

In this study, overall AMR was significantly lower in the CAdE colonoscopy arm (13.89% vs. 40.00%,  $P < 0.0001$ ). This AMR is comparable to the reduction in AMR seen when utilizing FUSE technology (7% to 20%)<sup>3,4</sup>. This indicates missed diagnosis by lack of recognition might be an equally important issue as non-visualization. Moreover, results in this study are comparable with that of Western and Japanese studies, which similarly show a 30% to 41%<sup>3,4</sup> in the routine colonoscopy groups when compared to an AMR of 40% in our white light first group.

AMR was found to be significantly lower for both diminutive ( $< 5\text{mm}$ ) and small adenomas (5-9mm) in the CAdE colonoscopy group when compared to the routine colonoscopy group in this tandem study. Notably, CAdE here is shown to reduce miss rate in the ascending, transverse and descending colon, whereas FUSE and similar approaches which aim at enlarging the visual field mainly seem to primarily provide benefits in the right colon where the folds are deeper<sup>1,3,4</sup>. Consistent with our previous studies, CAdE reduces miss rate of non-pedunculated adenomas. However, there was no statistical difference in miss rate of large adenomas, advanced adenomas and sessile serrated adenoma/polyp (SSA/P), a fact likely due to limited sample size and corresponding low statistical power for these specific groups of polyps. Similar findings were seen in the J-FUSE study<sup>3</sup>. Moreover, no difference in miss rates of SSA/Ps is suggested due to low numbers and insufficient powering. It is also possible that the learning images used to train the CAdE system were limited by the experience of average endoscopists. An exclusive study demonstrated the per-image-sensitivity of this CAdE system on small SSA/P was 80%, which is lower than 94%, the per-image sensitivity of the conventional adenomas and non-neoplastic polyps<sup>3,4</sup>. Future improvement in CAdE should be directed to sensitively and specifically detect hard-to-detect SSA/Ps collected among more extensive sources. Further studies should also look at AMR for advanced adenoma and SSA/Ps, with a larger sample size aimed at detecting a statistically significant difference.

In this study, some missed adenomas did not appear on the screen during the first pass, and were detected due to additional exposure during the second pass, a situation that cannot be counted as a contribution from the CAdE system. Therefore, we performed a post-hoc video analysis and tried to measure a more ‘specific’ AMR for only visible polyps, which we defined as AMR-V. Hence, we could compare CAdE and the naked human eye exclusively on visible lesions. AMR-V represents the maximal possibility that the CAdE could help to decrease the miss rate, only 1.59% visible adenomas were missed by CAdE colonoscopy whereas 24.21% of visible polyps were missed in the routine colonoscopy ( $p < 0.001$ ) group. Furthermore, among the 23 initially missed visible adenomas by endoscopists, 10 (10/23, 43.48%) of them were successfully detected by CAdE system in post-hoc video analysis. These data indicate that half of the initially missed visible adenomas could be addressed directly by CAdE’s alert. This study is the first study to analyze a specific AMR for visible lesions, which overcomes a common limitation of previous FUSE tandem studies<sup>3,4</sup> which did not distinguish whether the additional detection of specific polyps was actually due to its wider viewing angle cameras or not. Noticeably, not only the miss rate of visible adenoma/polyp is higher in the Routine-CAdE group, but also the miss rate of invisible adenoma/polyp is higher in the Routine-CAdE group. To further break down this analysis on each operating endoscopist (Table S4), the result is very similar

among them. This indicates that endoscopists can focus more on exposing colon mucosa, because of the enhanced CADe signal on the exposed polyps. Thus, it indicates that CADe not only increases polyps detection in the visual field, but also increased the exposure of more polyps.

PDR, APC and PPC were found to be significantly higher in the CADe colonoscopy group when compared to routine white light colonoscopy in both first and second passes. These findings are consistent with previous comparative studies which demonstrated the positive impact of CADe. The 67 total consistent false detections in the CADe colonoscopy was consistent with our previous studies, in which wrinkled mucosa consisted the largest portion of false positive lesions. Moreover, the similar withdrawal time (excluding the biopsy time) further demonstrated that the false alarm rate is low enough that withdrawal times are not affected during CADe withdrawal. (Table S1)

It should be noted that to alert visible lesions is only one of application scenario of computer vision technology. Only with high-level manipulation of endoscopists can this technology play its best role. Therefore, another important application of AI during colonoscopy is to alert suboptimal inspection, including endoscopists' ignorance to inspect the back of folds and flexures, ignorance to fully inflate the lumen, ignorance to clean the lens and absorb the liquid, unstable manipulation as well as too fast withdraw. Thus, the CADe system with a combination of suboptimal inspection alert system as well as new optical models or accessories (such as FUSE and Endocuff) which enlarge visual field, can further increase the detection of colon cancer and any precancerous lesions.

This study has several limitations. First, AMR obtained in the tandem study cannot reflect the absolute miss rate, because some lesions might have been missed again in the second pass. For those possible missed polyps/adenomas detected by post-hoc video analysis with CADe in the first pass, but not detected in the second pass during the study, there's no reliable way to further characterize these lesions without a third colonoscopy. However, the 34.78% and 26.49% ADR in CADe colonoscopy and routine colonoscopy are the highest in Chinese data<sup>35 36 37 38</sup> in a population younger than a guideline-recommended screening population, thus we believe the result is meaningful and representative.

Second, this open label trial might introduce subjective bias, as endoscopists might put more effort in when being observed or might relax and rely on the CADe in non-blinded trials leading to an overestimation or underestimation of the effectiveness of CADe system. However, the 34.78% and 26.49% ADR for either CADe colonoscopy or routine colonoscopy was consistent with our double-blinded study<sup>5</sup>, in which the same endoscopy models were used, and the withdrawal time was also similar in two groups, which could be an indirect marker of attentiveness. In addition, the overall ADR, PDR, APC and PPC in both passes were not different between CADe colonoscopy first group and routine colonoscopy first group, which indicates that the possibility of missing adenomas or polyps is not biased after 2 passes and independent of the order. These findings suggest that there is likely minimal subjective bias seen in the endoscopists used in this study.

Third, as tandem colonoscopy in each patient was performed by the same endoscopist, there might be "one and done phenomenon"<sup>39 40 41</sup>, whereby endoscopists may be less careful when examining the rest of the colon after identifying a single adenoma and might be less attentive in the second pass procedure. However, a single-endoscopist endoscopist design may introduce minimal inter-observer variation, which is a goal for this study.

Fourth, we did not restrict the study population to screening-only participants according to guidelines, thus the results might not be generalizable to a typical screening population in which the absolute number of adenomas is higher.

Fifth, only skilled endoscopists were allowed to participate in this study as colonoscopy performers, thus the results might not be generalizable to junior endoscopists or trainees. How this CAdE system will affect AMR as a clinical routine in practice is less clearly demonstrated in this study, because only 3 endoscopists participated. Reproducing the findings among more endoscopists of varying experience would appear warranted.

Sixth, the judgments made by 3-expert panel who reviewed the video record were not a gold standard as pathology and thus might introduce subjective bias.

Finally, the new generation models with image enhanced technologies such as Linked Color Imaging (LCI) by Fujifilm could offer better visualization<sup>42</sup> and have the potential to supersede white light colonoscopy, thus the effectiveness of CAdE using the latest models of endoscope should be further investigated.

In conclusion, the results from this study suggest a significantly lower AMR when utilizing a CAdE technology when compared to routine white light colonoscopy. The detection of diminutive and small adenomas with non-advanced histology and non-pedunculated shape could be effectively improved by CAdE colonoscopy. The CAdE colonoscopy has the potential to improve the clinical efficacy of screening and surveillance colonoscopy, with the goal of further decrease the risk of interval colorectal cancer development.

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**Table 1. Baseline information**

| Characteristics                                  | Routine-CADe group<br>(N = 185) | CADe-Routine group<br>(N = 184) | P* value |
|--------------------------------------------------|---------------------------------|---------------------------------|----------|
| Age, mean (SD)                                   | 47.19 (10.38)                   | 47.72 (10.82)                   | 0.628    |
| BMI, mean (SD)                                   | 23.21 (3.15)                    | 23.19 (3.02)                    | 0.939    |
| Indication                                       |                                 |                                 | 0.42     |
| Screening, n (%)                                 | 55 (29.73)                      | 58 (31.52)                      |          |
| Symptomatic, n (%)                               | 117 (63.24)                     | 107 (58.15)                     |          |
| Surveillance, n (%)                              | 13 (7.03)                       | 19 (10.33)                      |          |
| Sex                                              |                                 |                                 | 0.467    |
| Female, n (%)                                    | 99 (53.51)                      | 91 (49.46)                      |          |
| Male, n (%)                                      | 86 (46.49)                      | 93 (50.54)                      |          |
| BMI category                                     |                                 |                                 | 0.593    |
| < 25, n (%)                                      | 132 (71.35)                     | 135 (73.37)                     |          |
| 25 <= BMI < 30, n (%)                            | 51 (27.57)                      | 45 (24.46)                      |          |
| >= 30, n (%)                                     | 2 (1.08)                        | 4 (2.17)                        |          |
| Procedure time                                   |                                 |                                 | 0.831    |
| AM, n (%)                                        | 96 (51.89)                      | 98 (53.26)                      |          |
| PM, n (%)                                        | 89 (48.11)                      | 86 (46.74)                      |          |
| Endoscope                                        |                                 |                                 | 0.5      |
| EC-590ZW/M                                       | 2 (1.08)                        | 0 (0.00)                        |          |
| EC-L590WM                                        | 17 (9.19)                       | 19 (10.33)                      |          |
| EC-580RD/M                                       | 1 (0.54)                        | 0 (0.00)                        |          |
| EC-590WM                                         | 2 (1.08)                        | 1 (0.54)                        |          |
| EC-L590ZM                                        | 163 (88.11)                     | 164 (89.13)                     |          |
| Anesthesia #                                     |                                 |                                 | Na       |
| No, n (%)                                        | 0 (0.00)                        | 0 (0.00)                        |          |
| Yes, n (%)                                       | 185 (100.00)                    | 184 (100.00)                    |          |
| Boston Score, mean (SD)                          | 7.19 (1.42)                     | 7.11 (1.40)                     | 0.563    |
| Boston Score Rank                                |                                 |                                 | 0.846    |
| Inadequate (Sum < 6.0 or anyone < 2.0), n (%)    | 24 (12.97)                      | 25 (13.59)                      |          |
| Adequate (Sum >= 6.0 and everyone >= 2.0), n (%) | 161 (87.03)                     | 159 (86.41)                     |          |

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.

No Polyp Withdrawal time, Withdrawal time during those colonoscopies where no polyp was detected or removed.

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test.

# Anesthesia was administered with midazolam, fentanyl by an anesthesiologist there to monitor for complications.

**Table 2. Analysis of per-lesion miss rate**

|                         | Routine-CADe group<br>(n = 185) | CADe-Routine group<br>(n = 184) | P* value |
|-------------------------|---------------------------------|---------------------------------|----------|
| Adenoma                 |                                 |                                 |          |
| Detected at first pass  | 72                              | 124                             |          |
| Detected at second pass | 48                              | 20                              |          |
| Miss rate, %            | 40.00(31.23-48.77)              | 13.89(8.24-19.54)               | <0.0001  |
| Polyp                   |                                 |                                 |          |
| Detected at first pass  | 132                             | 248                             |          |
| Detected at second pass | 112                             | 37                              |          |
| Miss rate, %            | 45.90(39.65-52.15)              | 12.98(9.08-16.88)               | <0.0001  |
| Advanced adenoma        |                                 |                                 |          |
| Detected at first pass  | 9                               | 1                               |          |
| Detected at second pass | 3                               | 1                               |          |
| Miss rate, %            | 25.00(0.50-49.50)               | 50.00(-19.30-119.30)            | 1        |
| SSA/P                   |                                 |                                 |          |
| Detected at first pass  | 1                               | 0                               |          |
| Detected at second pass | 2                               | 1                               |          |
| Miss rate, %            | 66.67(13.33-120.01)             | 100.00(100.00-100.00)           | 0.9978   |

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test.

**Table 3. Clinicopathologic characteristics of adenomas missed with Routine and CADe colonoscopy**

|                  | Routine-CADe group<br>(n = 185) | CADe-Routine group<br>(n = 184) | P* value |
|------------------|---------------------------------|---------------------------------|----------|
| Size, mm         |                                 |                                 |          |
| <5               | 39.66(27.07-52.25)              | 13.11(4.64-21.58)               | 0.0015   |
| 5-9              | 46.94(32.97-60.91)              | 13.75(6.20-21.30)               | <0.0001  |
| >=10             | 15.38(-4.23-34.99)              | 33.33(-20.01-86.67)             | 0.4842   |
| Morphologic type |                                 |                                 |          |
| Pedunculated     | 23.08(0.18-45.98)               | 10.00(-8.59-28.59)              | 0.4241   |
| Not Pedunculated | 42.45(33.04-51.86)              | 14.18(8.27-20.09)               | <0.0001  |
| LST              | 0.00(0.00-0.00)                 | Na                              |          |
| Location         |                                 |                                 |          |
| Cecum            | 50.00(-19.30-119.30)            | 0.00(0.00-0.00)                 | 0.5473   |
| Ascending colon  | 39.13(19.18-59.08)              | 6.67(-2.26-15.60)               | 0.0095   |
| Transverse colon | 45.16(27.64-62.68)              | 16.33(5.98-26.68)               | 0.0065   |
| Descending colon | 40.91(20.36-61.46)              | 12.50(-0.73-25.73)              | 0.0364   |
| Sigmoid colon    | 40.62(23.60-57.64)              | 18.18(5.02-31.34)               | 0.0514   |
| Rectum           | 20.00(-4.79-44.79)              | 20.00(-15.06-55.06)             | 1        |

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test.

**Table 4. Miss rate of visible and invisible adenomas and polyps**

|         | Routine-CADe group<br>(n = 185) | CADe-Routine group<br>(n = 184) | P *value |
|---------|---------------------------------|---------------------------------|----------|
| AMR V   | 0.2421                          | 0.0159                          | <0.001   |
| PMR- V  | 0.3089                          | 0.0236                          | <0.001   |
| AMR-INV | 0.2500                          | 0.1268                          | 0.016    |
| PMR-INV | 0.2707                          | 0.1111                          | <0.001   |

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test.

|                                    | Routine-CADe group<br>(N = 185) | CADe-Routine group<br>(N = 184) | P value | Odds ratio | Confidence interval | Interval |
|------------------------------------|---------------------------------|---------------------------------|---------|------------|---------------------|----------|
| Whole Process                      |                                 |                                 |         |            |                     |          |
| PDR                                | 0.5514                          | 0.6359                          | 0.099   | 1.421      | 0.936-2.157         | 1.221    |
| ADR                                | 0.3568                          | 0.4239                          | 0.186   | 1.327      | 0.872-2.018         | 1.146    |
| Average Number of Detected Polyp   | 1.3189                          | 1.5489                          | 0.065   | 1.174      | 0.990-1.393         | 0.403    |
| Average Number of Detected Adenoma | 0.6486                          | 0.7826                          | 0.129   | 1.207      | 0.947-1.537         | 0.59     |
| First Pass                         |                                 |                                 |         |            |                     |          |
| PDR                                | 0.3784                          | 0.5598                          | 0.001   | 2.089      | 1.378-3.167         | 1.789    |

**Table 5. ADR, PDR, APC and PP**

|                                    |        |        |        |       |             |       |
|------------------------------------|--------|--------|--------|-------|-------------|-------|
| ADR                                | 0.2649 | 0.3478 | 0.085  | 1.48  | 0.948-2.312 | 1.364 |
| Average Number of Detected Polyp   | 0.7135 | 1.3478 | <0.001 | 1.889 | 1.529-2.333 | 0.804 |
| Average Number of Detected Adenoma | 0.3892 | 0.6739 | <0.001 | 1.732 | 1.295-2.315 | 1.02  |
| Second Pass                        |        |        |        |       |             |       |
| PDR                                | 0.3784 | 0.1902 | <0.001 | 0.386 | 0.240-0.619 | 0.379 |
| ADR                                | 0.1838 | 0.1087 | 0.043  | 0.542 | 0.299-0.982 | 0.683 |
| Average Number of Detected Polyp   | 0.6054 | 0.2011 | <0.001 | 0.332 | 0.229-0.482 | 0.253 |
| Average Number of Detected Adenoma | 0.2595 | 0.1087 | 0.001  | 0.419 | 0.249-0.706 | 0.457 |

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test

**Table 6. Analysis by patient findings**

|                                            | Routine-CADe group<br>(n = 185) | CADe-Routine group<br>(n = 184) | P* value |
|--------------------------------------------|---------------------------------|---------------------------------|----------|
| Patients with adenoma                      |                                 |                                 |          |
| Detected at first pass                     | 49                              | 64                              |          |
| Detected at second pass                    | 34                              | 20                              |          |
| Detected at second pass for the first time | 17                              | 14                              |          |
| Detection rate at first pass, %            | 26.49(20.13-32.85)              | 34.78(27.90-41.66)              | 0.0846   |
| Miss rate, %                               | 25.76(19.46-32.06)              | 17.95(12.40-23.50)              | 0.258    |

\* P value from  $\chi^2$  test (or Fisher's exact test, as appropriate) or t-test.

AF-22/01.0



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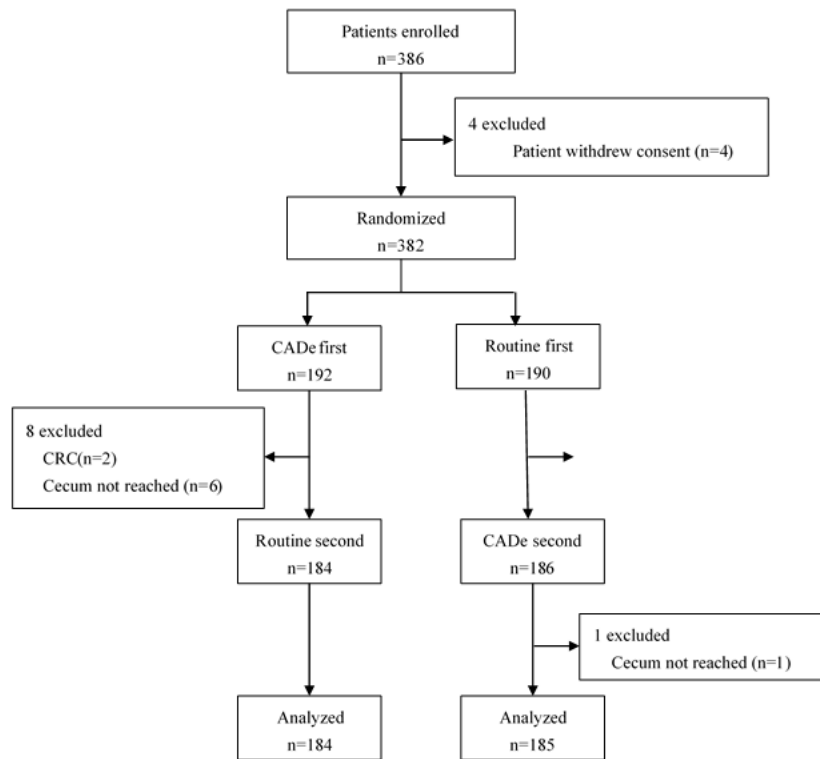
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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------|----------|
| 项目名称 Project                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 基于深度学习技术的结肠镜下结直肠息肉实时识别系统辅助下对结直肠腺瘤诊断能力的研究 |                                                              |          |
| 申请类别 Classification                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 临床科研                                     | 研究类型 Research Type                                           | 非干预性研究   |
| 审查类型 Review Categories                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 初始审查                                     | 审查方式 Review Pattern                                          | 快速审查     |
| 申请科室 Department                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 消化内科                                     | 主要研究者/职称 PI/Title                                            | 李良平/主任医师 |
| 审评材料 Form be handed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                          |                                                              |          |
| <input checked="" type="checkbox"/> 研究方案(版本号 1.0 日期 2019.3)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                          | <input checked="" type="checkbox"/> 知情同意书(版本号 1.0 日期 2019.3) |          |
| <input checked="" type="checkbox"/> 研究者资格                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                          | <input checked="" type="checkbox"/> 其它文件                     |          |
| 审查结果 Decision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                          |                                                              |          |
| 快审委员: 刘洲、何林<br>快审结果: 同意                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                          |                                                              |          |
| 审评意见 Comments:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                          |                                                              |          |
| <p>根据卫计委《涉及人的生物医学研究伦理审查办法》(2016)、CFDA《药物临床试验质量管理规范》(2003)、《医疗器械临床试验规定》(2004)、《药物临床试验伦理审查工作指导原则》(2010)、WMA《赫尔辛基宣言》(2013)和 CIOMS《人体生物医学研究国际道德指南》(2002)的伦理原则,经本伦理委员会审查,意见如下:</p> <p>请遵循伦理委员会批准的方案开展临床研究,保护受试者的健康与权利。</p> <p>请遵循《人类遗传资源管理暂行办法》(国办发〔1998〕36号)和《人类遗传资源采集、收集、买卖、出口、出境审批行政许可事项服务指南》,属行政许可事项规定范畴的研究,获得伦理批件后应按相关规定进行审批,经中国人类遗传资源管理办公室批准后及时将批准文件交伦理委员会备案后方可实施。</p> <p>研究过程中若变更主要研究者,对临床研究方案、知情同意书、招募材料等的任何修改,请申请人提交修正案审查申请。定期跟踪审查频率为12个月,请研究者按照跟踪审查频率,在截止日期前一个月内按时提交研究进展报告;发生严重不良事件,请申请人及时提交严重不良事件报告及随访总结报告。当出现任何可能显著影响研究进行、或增加受试者危险的情况时,请申请人及时向伦理委员会提交书面报告。</p> <p>研究纳入了不符合纳入标准或符合排除标准的受试者,符合中止试验规定而未让受试者退出研究,给予错误治疗或剂量,给予方案禁止的合并用药等没有遵从方案开展研究的情况;或可能对受试者的权益/健康、以及研究的科学性造成不良影响等情况,请研究者提交违背方案报告。</p> <p>申请人暂停或提前终止研究,请及时提交暂停/终止研究报告。</p> <p>完成临床研究,请申请人提交结题报告。自批准之日起半年内未启动项目者,批件自动废止;申请人需向伦理委员会重新提交伦理审查申请。</p> |                                          |                                                              |          |
| 主任委员签名 Signature:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                          |                                                              |          |
| 日期 Dates:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                          | 2019.4.5.                                                    |          |

注: ☒ 表示选择该项

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**What you need to know:**

**Background and Context:** Up to 30% of adenomas might be missed during screening colonoscopy. Computer-aided detection (CAdE) systems, based on deep learning, might reduce rates of missed adenomas by displaying visual alerts that identify precancerous polyps on the endoscopy monitor in real time.

**New Findings:** CAdE colonoscopy reduced the overall miss rate of adenomas by endoscopists performing white-light endoscopy.

**Limitations:** Larger studies are needed to provide external validation of these findings.

**Impact:** Routine use of CAdE might reduce the incidence of interval colon cancers.

**Lay Summary:** This study describes use of a computer-aided detection system to aide endoscopists in detection of polyps during colonoscopies.