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Real-time use of artificial intelligence (CADEYE) in colorectal cancer surveillance of patients with Lynch syndrome—A randomized controlled pilot trial (CADLY)

Robert Hüneburg[1,2] | **Karolin Bucksch**[3] | **Friederike Schmeißer**[1,2] | **Dominik Heling**[1,2] | **Tim Marwitz**[1,2] | **Stefan Aretz**[1,4] | **Dominik J. Kaczmarek**[1,2] | **Glen Kristiansen**[1,5] | **Oliver Hommerding**[1,5] | **Christian P. Strassburg**[1,2] | **Christoph Engel**[3] | **Jacob Nattermann**[1,2]

[1]National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany

[2]Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany

[3]University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany

[4]Institute of Human Genetics, University of Bonn, Bonn, Germany

[5]Institute of Pathology, University Hospital Bonn, Bonn, Germany

Correspondence

Robert Hüneburg, Department of Internal Medicine I, National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Venusberg-Campus 1, Bonn 53127, Germany.
Email: robert.hueneburg@ukbonn.de

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Abstract

Background: Lynch syndrome (LS), an autosomal dominant disorder caused by pathogenic germline variants in DNA mismatch repair (MMR) genes, represents the most common hereditary colorectal cancer (CRC) syndrome. Lynch syndrome patients are at high risk of CRC despite regular endoscopic surveillance.

Objective: Our aim was to investigate the diagnostic performance of artificial intelligence (AI)-assisted colonoscopy in comparison to High-Definition white-light endoscopy (HD-WLE) for the first time.

Methods: Patients ≥18 years with LS, with a pathogenic germline variant (*MLH1*, *MHS2*, *MSH6*), and at least one previous colonoscopy (interval 10–36 months) were eligible. Patients were stratified by previous CRC and affected MMR gene with a 1:1 allocation ratio (AI-assisted vs. HD white-light endoscopy) in this exploratory pilot trial.

Results: Between Dec-2021 and Dec-2022, 101 LS patients were randomised and 96 patients were finally analyzed after exclusion of 5 patients due to insufficient bowel preparation. In the HD-WLE arm, adenomas were detected in 12/46 patients compared to 18/50 in the AI arm (26.1% [95% CI 14.3–41.1] vs. 36.0% [22.9–50.8]; $p = 0.379$). The use of AI-assisted colonoscopy especially increased detection of flat adenomas (Paris classification 0-IIb) (examinations with detected flat adenomas: 3/46 [6.5%] vs. 10/50 [20%]; $p = 0.07$; numbers of detected flat adenomas: 4/20 vs. 17/30, $p = 0.018$). The median withdrawal time did not differ significantly between HD-WLE and AI (14 vs. 15 min; $p = 0.170$).

Conclusion: We here present first data suggesting that real-time AI-assisted colonoscopy is a promising approach to optimize endoscopic surveillance in LS patients, in particular to improve the detection of flat adenomas.

KEYWORDS
endoscopy

INTRODUCTION

Lynch syndrome, an autosomal dominant disorder caused by pathogenic germline variants in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*), represents the most common hereditary CRC syndrome.[1] Current analyses proposed one in 279 individuals of the general population to be a carrier of a pathogenic germline variant.[2] Based on these estimates, about 300.000 individuals in Germany and approximately 1.000.000 in the United States are expected to have LS.

Carriers of pathogenic variants are at high risk of CRC with a cumulative incidence of up to 70% by the age of 70 despite regular endoscopic surveillance.[3] Although the prevalence of polyps in LS seems to be similar to the general population, the pathway to CRC appears to be accelerated, underpinning the importance of regular colonoscopy surveillance.[4] Furthermore, small and flat adenomas are especially prone to harbor high-grade dysplasia in LS.[5] Colorectal carcinogenesis is complex and not completely understood. Adenomas seem to be the most important precursor lesion,[4] but alternative pathways are also discussed.[6]

Colonoscopy quality depends on the experience of the endoscopist, procedural factors (e.g. bowel preparation) and certain morphological characteristics of the lesion.[7] Thus, a significant number of adenomas are still missed during colonoscopy, with reported adenoma miss-rates in LS ranging from 12% to 62%. In particular, small lesions as well as flat adenomas which are characteristic for LS are often overlooked.[8,9]

The National Comprehensive Cancer Network recommends the use of high-definition white-light endoscopes (HD-WLE) in patients with LS to ensure the detection of small lesions with a screening interval of 1–2 years.[10]

Recent data indicate that artificial intelligence (AI)-assisted colonoscopy, also known as computer-aided detection, may help to increase both adenoma detection rate (ADR) as well as polyp detection rate in the general population.[11] Whether this also holds true for LS patients is unclear at the moment as the use of AI-assisted colonoscopy in LS has only been described in a single case report to date.[12]

Therefore, the aim of the present study was to assess the adenoma detection rate with and without the use of AI-assisted colonoscopy in Lynch patients in an exploratory setting.

Key Summary

Summarize the established knowledge on this subject

- Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome
- High risk to develop CRC despite regular surveillance
- Current European Society for Gastrointestinal Endoscopy guideline recommends high-definition white light endoscopy
- Wide variation of adenoma detection rate between 10% and 22%

What are the significant and/or new findings of this study?

- First study to evaluate artificial intelligence assisted colonoscopy in LS
- High adenoma detection rate in both study arms (HD white-light endoscopy (HD-WLE) 26.1%; artificial intelligence (AI) 36%)
- Higher detection rate of flat adenomas using AI
- Similar examination times in both study arms

MATERIALS AND METHODS

Study design and setting

The study was approved by the local ethics committee [488/20; date of registration 30-Nov-2020] and was registered on the German Clinical Trials Register (www.drks.de; DRKS00023157; date of registration 9-Dec-2020). The trial start and first patient included was on 10-Dec-2020.

This explorative, randomized controlled trial aimed to determine adenoma detection rates (ADR) under HD-WLE with and without the use of real-time artificial intelligence (CADEYE) in patients with LS at the National Center for Hereditary Tumor Syndromes in Bonn, Germany. The study is reported in accordance with the Consolidated Standards of Reporting Trials statement reporting randomized controlled trials.[13]

Patients

Consecutive asymptomatic patients undergoing regular endoscopic surveillance for LS were approached to participate in the trial. Patients were eligible if they were aged 18 years or older and carriers of a (likely-) pathogenic variant in *MLH1*, *MSH2* or *MSH6*. Patients had to have already participated in endoscopic surveillance with at least one previous colonoscopy performed between the last 10–36 months. Exclusion criteria were previous extensive colorectal surgery (proctocolectomy or colectomy with ileorectal anastomosis) or current pregnancy. Eligible patients were informed about the study aims, procedures and potential risks by the endoscopist. After sufficient time to consider participation (time span of 0–28 days), written informed consent was obtained.

Randomization and allocation concealment

Patients were randomized with 1:1 allocation ratio to the two trial arms. Randomization was stratified by previous colorectal surgery (yes/no) and affected MMR gene (*MLH1/MSH2/MSH6*). Before start of recruitment, the responsible study biometrician generated the randomization list centrally. Randomization used computer-generated random numbers and employed a random permuted block design. Sealed opaque envelopes were prepared centrally by the study biometrician and were provided to the study center. Randomization was performed prior to the start of the procedure.

Endoscopic procedure

All patients were prepared with osmotic laxatives. The procedure was performed with or without deep sedation at the discretion of the endoscopist and patient. The endoscope was advanced to the (neo-) terminal ileum. After reaching the (neo-) terminal ileum, time measurement began and bowel preparation (Boston Bowel Preparation Scale [BBPS]) was assessed. Patients with insufficient bowel preparation (defined as a BBPS score <2 in any segment) were excluded from the final analysis.

When the patient was allocated to the AI group the AI system for polyp detection and characterization (EW10-EC02 CAD-EYE system from Fujifilm Japan) was running during withdrawal, whereas in the control group the AI system was shut off. High-definition technology (ELUXEO 7000 system, EC-760R-V/I colonoscope; Fujifilm, Japan) was used for all examinations. Participating endoscopists had extensive experience in LS endoscopic surveillance and were familiar with the Fujifilm 7000 system. Colonoscopy was performed by three endoscopists experienced (>1000 total colonoscopies and >300 colonoscopies in LS patients) in performing surveillance in LS patients.

All detected polyps were described by size (measured by an open biopsy forceps), anatomical location, and polyp shape according to the Paris classification. Endoscopists used LCI, BLI and the AI characterization mode to assess each lesion. Subsequently, the lesion was resected endoscopically by using standard polypectomy techniques. All lesions were sent in for histopathological diagnosis in a unique histopathology container. Retroflection in the rectum was mandatory. When the patient was allocated to HD-WLE, inspection on withdrawal was performed using HD-WLE.

The examination time was defined as the time spent on inspection (withdrawal time), excluding time for cleaning of the bowel and the time spent on polypectomy. All adverse events (AEs) related to the study intervention were recorded in the electronic case report form.

An experienced gastrointestinal pathologist, blinded for the endoscopic technique as well as the optical diagnosis of the lesions detected during colonoscopy, was designated to this study. Fixation was achieved by buffered 10% formalin. After fixation, the specimens were described and sectioned transversely into 3 mm slices. This allowed the identification of deep and lateral margins. Three or more levels were cut through each block and stained with hematoxylin and eosin.

Histological findings were reported according to the Vienna classification of gastrointestinal neoplasia.

Advanced adenoma was defined as an adenoma ≥10 mm, with villous morphology, or with high-grade dysplasia.

Study outcomes and definitions

The primary outcome measure of the study (adenoma detection rate/ADR) was defined as the number of examinations in which at least one adenoma is detected divided by the total number of endoscopic examinations. Secondary outcome measures were the total and mean number, size, morphology, and anatomical location of detected adenomas as well as sessile serrated lesions, median examination times and occurrence of AEs.

Sample size and statistical methods

This trial was performed with exploratory rather than confirmatory intention due to the wide variety of published ADR in LS patients between 10% and 22%.[7,14–16] Thus, no formal *a priori* sample size calculation was performed. The planned sample size of 100 patients (50 patients per treatment arm including 10% dropouts and invalid cases) was deemed large enough to obtain ADR estimates.

Exact Clopper-Pearson confidence intervals were calculated for detection rates. Group comparisons were performed using the Welch Two Sample *t*-test for continuous variables and Fisher Exact Test for categorical variables, respectively. All reported testing was two-sided. Due to the exploratory intention of the study, no correction for multiple testing was performed. Statistical analyses were carried out with R 4.1.1 for Windows (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org).

Patient and public involvement and role of the funding source

The study center was periodically monitored by a senior Clinical Research Associate of the Clinical Research Unit of the Clinical Study Core Unit of the University Hospital Bonn. The German patient advocacy group (www.semi-colon.de) was involved in study design and conduct of the study. Fujifilm Germany GmbH provided research equipment on loan for this study. A research grant was obtained by the medical faculty of the University Hospital Bonn (2020-FKS-03-E). The funder had no role in trial design, execution, data analysis, and interpretation, decision to submit paper or manuscript preparation. All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Between December 2021 and December 2022, 150 individuals with LS were assessed for eligibility of which 101 patients were enrolled in this trial. After excluding five patients (3 HD-WLE arm, 2 AI arm) due to insufficient bowel preparation (BBPS <2 in one segment), the final analysis included 96 patients, 46 in the control and 50 in the AI arm. Figure 1 shows the flowchart.

The two study arms did not differ significantly in terms of general patient characteristics. Almost half of all participants had a personal history of CRC (40 patients; 42%). A history of extracolonic cancer was documented in 28 patients (29%). In both groups the most common mutation type was *MSH2*, followed by *MLH1* and *MSH6*.

All patients had received at least one previous colonoscopy with a mean time since the previous surveillance colonoscopy of 17 months in the HD-WLE and 16.5 in the AI arm. In 20% of the previous colonoscopies at least one adenoma was detected. Baseline characteristics are shown in Table 1.

Primary outcome

Analysis for the primary outcomes is summarised in Table 2. The overall adenoma detection rate was 31.3% (95% CI 22.2%–41.5%). In the HD-WLE arm, adenomas were detected in 12/46 patients compared to 18/50 in the AI arm, corresponding to a higher ADR (26.1% [95% CI 14.3–41.1] vs. 36.0% [22.9–50.8]; $p = 0.379$) and mean number of adenomas detected per procedure (0.43 vs. 0.60) in AI-assisted colonoscopy.

Secondary outcomes

In the AI arm a higher proportion of the detected adenomas were completely flat (Paris classification 0-IIb) (17/30 [56.6%] vs. 4/20 [20%]; $p = 0.018$) and the number of examinations with detection of completely flat adenomas was higher in the AI arm compared to HD-WLE (3/46 [6.5%] vs. 10/50 [20%]; $p = 0.074$) (Table 3; Figure 2).

In addition, the rate of advanced adenomas detected was higher in AI-assisted colonoscopy (4/50 [8%] vs. 2/46 [4.3%]; $p = 0.063$) (Table 4).

In the subgroup of patients with a personal history of CRC, ADR was higher than in the patients without prior colon surgery, with higher adenoma detection rates in the AI arm in both subgroups (without prior CRC: AI 8/28 (28.6% [95% CI 13.2–48.7]) versus HD-WLE 6/28 (21.4% [95% CI 8.3–41.0]); with prior CRC: AI 10/22 (45.5% [95% CI 24.4–67.8]) versus HD-WLE 6/18 (33.3% [95% CI 13.3–59.0]). In patients without previous CRC no difference was

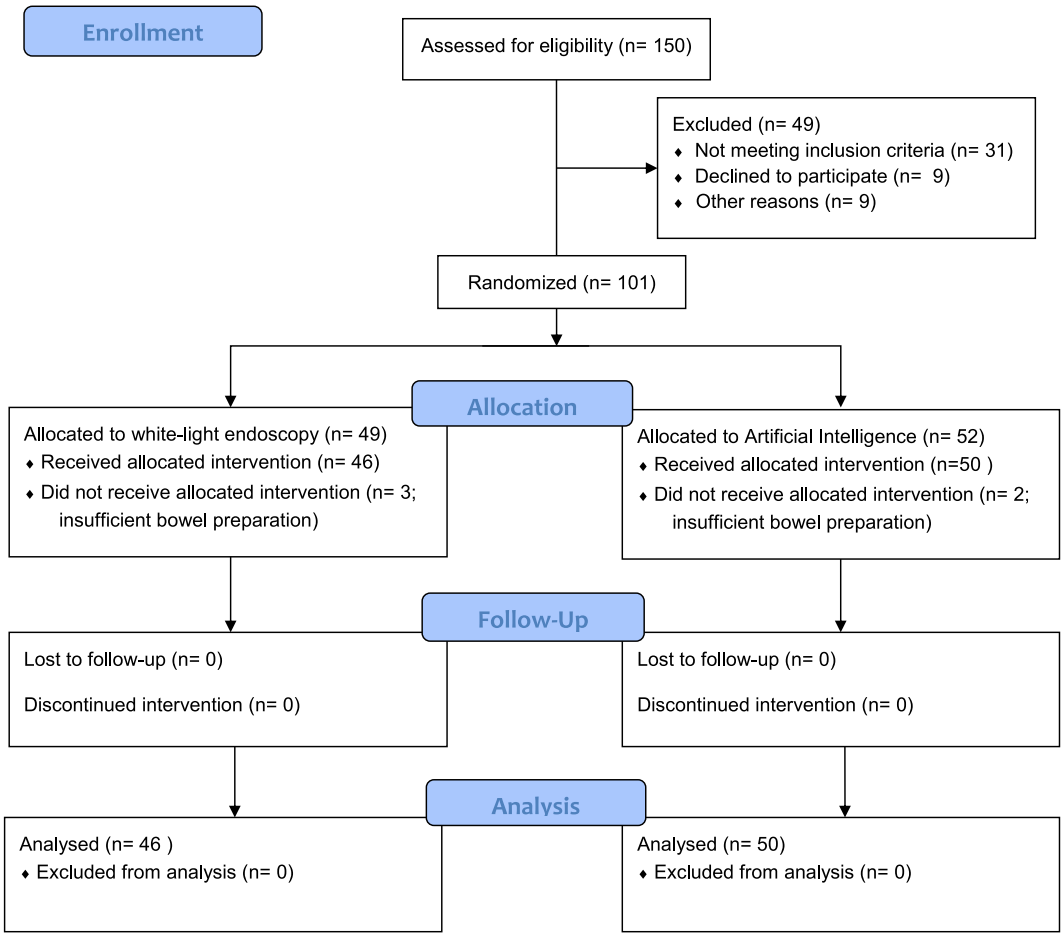

FIGURE 1 Consolidated Standards of Reporting Trials patient flowchart

TABLE 1 Baseline characteristics

	White-light endoscopy ($n = 46$)	Artificial Intelligence-assisted endoscopy ($n = 50$)	p-value
Age (years), mean ± SD; [range]	46.3 ± 11.8; [23, 70]	50.3 ± 11.9; [25, 75]	0.096
Female sex, *n* (%)	25 (54.4%)	30 (60.0%)	0.680
MLH1 pathogenic variant carriers, *n* (%)	17 (37.0%)	17 (34.0%)	0.832
MSH2 pathogenic variant carriers, *n* (%)	23 (50.0%)	25 (50.0%)	1
MSH6 pathogenic variant carriers, *n* (%)	6 (13.0%)	8 (16.0%)	0.777
Personal history of colorectal cancer, *n* (%)	18 (39.1%)	22 (44.0%)	0.682
Personal history of colon surgery, *n* (%)	18 (39.1%)	22 (44.0%)	0.682
Right hemicolectomy, *n* (%)	13 (72.2%)	14 (63.6%)	0.737
Transverse colon resection, *n* (%)	0 (0.0%)	1 (4.5%)	1
Left hemicolectomy, *n* (%)	1 (5.6%)	2 (9.1%)	1
Sigmoidectomy, *n* (%)	1 (5.6%)	1 (4.5%)	1
Rectal resection, *n* (%)	3 (16.7%)	4 (18.2%)	1
Personal history of extra-colonic cancers, *n* (%)	9 (19.6%)	19 (38.0%)	0.071
Age at index colonoscopy (years), mean ± SD; [range]	34.7 ± 9.1; [18, 55]	36.7 ± 12.0; [19, 74]	0.352
Elapsed time since last colonoscopy (months), mean ± SD	17.0 ± 5.6	16.5 ± 5.3	0.645
Adenoma detected during last colonoscopy, *n* (%)	8 (17.4%)	11 (22.0%)	0.617

TABLE 2 Polyp detection rates

	White-light endoscopy ($n = 46$)	Artificial Intelligence assisted endoscopy ($n = 50$)	p-value
Adenomas detected (*n*)	20	30	1
Examinations with adenomas (*n*)	12	18	0.379
Adenoma detection rate (%) with 95%-CI	26.1, 14.3–41.1	36.0, 22.9–50.8	
Examinations with advanced adenomas (*n*)	2	4	0.679
Advanced adenoma detection rate (%) with 95%-CI	4.3, 0.5–14.8	8.0, 2.2–19.2	
Polyps (*n*)	89	136	
Examinations with polyps (*n*)	34	42	0.315
Polyp detection rate (%) with 95%-CI	73.9, 58.9–85.7	84.0, 70.9–92.8	
Sessile serrated lesions detected (*n*)	5	8	1
Examinations with sessile serrated lesions (*n*)	4	7	0.528
Hyperplastic polyps (*n*)	38	41	0.064
Examinations with hyperplastic polyps (*n*)	22	22	0.838

noted in terms of adenoma localisation (right-sided adenomas 11/14 [78.6%] AI arm, 6/8 [75%] HD-WLE arm).

No significant difference was observed regarding size of adenomas detected in the both study arms (Table 3).

Regarding sessile serrated lesions, we did not observe any significant differences in terms of total numbers of detected lesions (5 vs. 8) and the number of examinations with sessile serrated lesions (4/46 [8.7%] vs. 7/50 [14%]; $p = 0.528$) between the AI and the HD-WLE study arm. Two colorectal cancers were detected in one patient in the AI group.

There were no significant differences in procedure-related factors (sedation, bowel preparation, procedure/withdrawal times) between the two groups (Table 5). No AEs were observed in any of the study arms.

DISCUSSION

This is the first randomised controlled trial comparing HD-WLE to AI for adenoma detection in Lynch surveillance. Although not significant,

TABLE 3 Neoplastic lesions

		White-light endoscopy (n = 46)	Artificial Intelligence assisted endoscopy (n = 50)	p-value
Adenomas detected (n)		20	30	1
Mean adenomas detected		0.43	0.60	
Adenomas detected (n)		20	30	1
Paris classification	Is-p (n)	3	2	0.377
	0-IIa (n)	13	11	0.082
	0-IIb (n)	4	17	0.018
	0-IIc (n)	-	-	
Examinations with completely flat adenomas (0-IIb) (n)		3	10	0.074
Flat (0-IIb) adenoma detection rate (%) with 95%CI		6.5, 1.4–17.9	20.0, 10.0–33.7	
Size of adenomas in mm, mean ± sd		4.9 ± 3.3	5.4 ± 4.4	0.626
Size	≤5 mm	15	22	
	6–9 mm	2	3	
	≥10 mm	3	5	
Colorectal cancers detected (n)		0	2	0.520

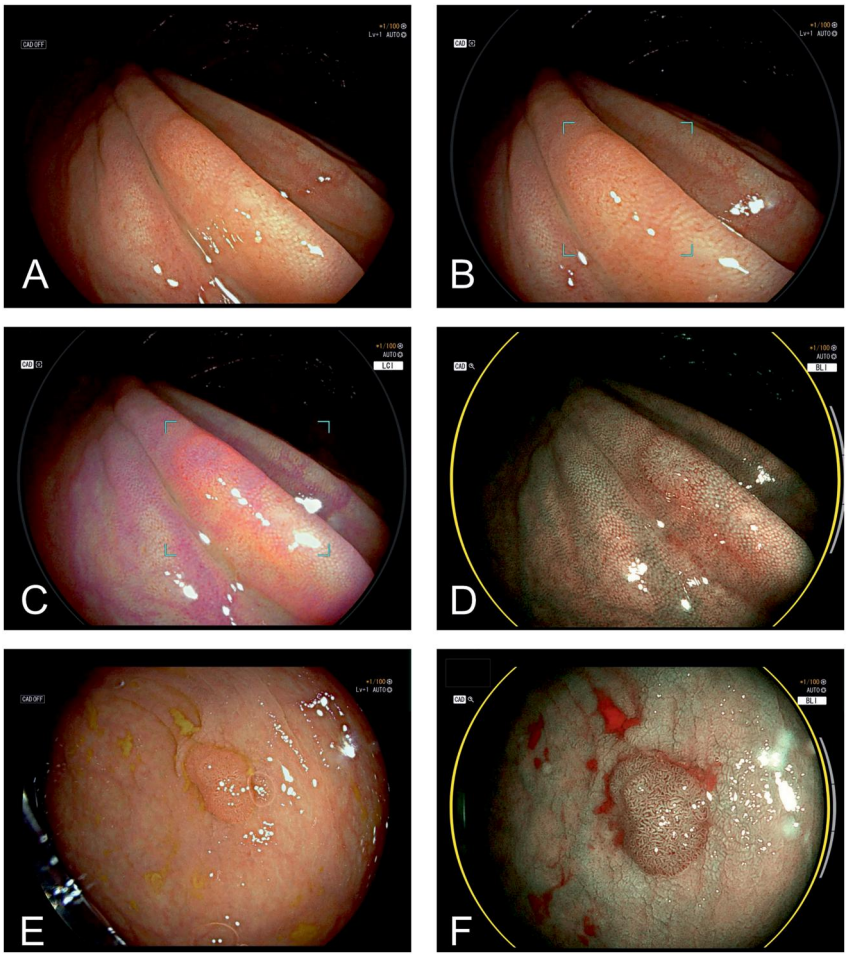

FIGURE 2 Images of a 3 mm flat adenoma (Paris classification 0-IIb) with high-definition white light endoscopy (a), with Artificial intelligence assisted detection (b), Linked Color imaging (c) and Blue Light Imaging with differentiation mode (d). Additionally, images of an advanced adenoma (Paris classification 0-IIa) with high-definition white light endoscopy (e) and Blue Light Imaging with differentiation mode (f).

TABLE 4 Advanced adenomas

	White-light endoscopy (n = 46)	Artificial Intelligence assisted endoscopy (n = 50)	Total
Advanced adenomas detected (n)	2	4	6
Size >10 mm	1	3[a]	4
High-grade dysplasia	1	1[a]	2
Villous histology[b]	0	1	1

[a]One lesion was larger than 10 mm with high-grade dysplasia.

[b]the definition of advanced adenoma was changed during the course of the study according to new published European Society for Gastrointestinal Endoscopy guidelines.[28] Here, we use the definition as defined in the study protocol.

TABLE 5 Colonoscopy characteristics

	White-light endoscopy (n = 46)	Artificial Intelligence assisted endoscopy (n = 50)	p-value
Complete colonoscopy (n)	46	50	1
Sedation			0.479
none	1	0	
Propofol	45	50	
Butylscopolamine	3	7	0.321
Procedure time in min, mean ± sd	21.1 ± 5.8	22.0 ± 5.3	0.425
Caecal intubation time in min, mean ± sd	7.1 ± 4.1	7.0 ± 3.5	0.891
Withdrawal time in min, mean ± sd	14.0 ± 3.5	15.0 ± 3.7	0.170
Boston bowel preparation scale ≥2 in every segment	46	50	1
no. of adverse events - baseline	0	0	1

the use of AI resulted in an increase of the adenoma detection rate and mean number of adenomas per patient suggesting for the first time that even in a high-risk population under regular surveillance, the quality of colonoscopy can be improved by using AI.

Adenomas are considered to represent the main precursors of CRC in LS. Due to the accelerated progression from adenoma to CRC in LS, high ADR is particularly important in these patients to minimize the risk of carcinoma development. Accordingly, intensified surveillance strategies with colonoscopies every one to 2 years have been shown to reduce both CRC incidence and CRC-associated mortality.[17–19] However, several studies have shown that a relevant proportion of adenomas are missed even when examinations are performed by experienced endoscopists. This is especially true for flat lesions, which are typical for LS.[9] These missed adenomas are considered a possible reason why patients with LS are at very high risk for post-colonoscopy CRC with a cumulative 10-year incidence of up to 8% despite endoscopic surveillance.[6,7]

Therefore, there is an ongoing clinical need to develop and evaluate new endoscopic techniques that may enable to optimize the detection of adenomas in high-risk patient groups such as LS patients.

In recent years, several clinical trials in the general population have demonstrated that AI-assisted colonoscopy is a promising approach, showing significant improvement in the detection of polyps and adenomas compared with standard white light endoscopy.[20–23] In the present work, we show that this may also apply to high-risk patient groups such as LS patients. However, it should be noted here that despite a profound increase in ADR in the AI group compared with the HD-WLE group, overall ADR was not significantly different between the two groups. This is most likely due to the relatively small sample size, reflecting the exploratory nature of our study. Moreover, we already achieved a high ADR of 26% in the WLE group, leading to less space for improvement. A certain strength of our study is that it reflects a real-world surveillance scenario by including a high proportion of patients with a history of colorectal surgery and a previous surveillance colonoscopy 10–36 months ago.

AI-assisted colonoscopy detected more completely flat (0-IIb) adenomas than high-definition colonoscopy in our study. These lesions are characteristic of LS and previous studies have shown that flat adenomas are more likely to be missed.[9] Therefore, our AI system may help improve the detection of such flat polyps that are easily

missed during colonoscopy. The fact that three of these flat adenomas were already advanced adenomas may support the clinical significance of this finding although this should be interpreted with caution due to the limited sample size and the high interobserver variability reported for the assessment of the Paris classification.[24]

The improvement of polyp detection by artificial intelligence may lead to an increased detection of clinically irrelevant lesions. However, in our study, no significant difference was found in the number of hyperplastic lesions detected between the two study groups.

It has been shown that patient-related factors (age, gene, gender, previous CRC) are associated with ADR and risk of CRC.[25] In our study, the patient groups did not differ significantly with respect to these parameters. In addition, procedure related factors such as insertion and withdrawal time, cecal intubation rate and BBPS score are factors that have been shown to affect ADR.[7,26] In our study, only patients with BBPS ≥2 in every segment were included. Furthermore, complete colonoscopy was achieved in all patients. In terms of insertion and withdrawal time, patient groups did not differ significantly, suggesting that AI is not time consuming but might enhance ADR.

Potential limitations of this study must be acknowledged. Most importantly, we did not perform a sample size calculation but conducted an exploratory study. This approach was chosen for the following reasons. First, a large variance is found in published studies regarding ADR for HD-WLE colonoscopy in LS (10%–26%).[14–16] Second, based on previously published data, no valid estimate of the potential effect of AI-based colonoscopy could be made because published data varied considerably even in the general population, although AI outperformed standard WL endoscopy in almost all studies.[20–23] Third, to our knowledge, no studies have been performed in cohorts encompassing a relevant number of patients with a history of colorectal surgery, which further complicated a valid case number estimate. For this reason, we opted for an exploratory study design. These data must now be validated in a prospective randomized multicentre study. Based on our data, we calculated a sample size of 362 patients per study arm (CI 95%, power 80%; calculated using PASS 11) will be needed.

Another possible limitation could be that only experienced endoscopists with strong expertise in LS surveillance performed all examinations. Thus, based on our data, no conclusions can be drawn about the possible effect of AI support in less experienced examiners. However, the current guideline by the European Society for Gastrointestinal Endoscopy emphasizes that patients with LS should be monitored in dedicated departments with appropriate expertise, which is ensured in our study.[27]

In conclusion, we here present first data suggesting that real-time AI-assisted colonoscopy is a promising approach to optimize endoscopic surveillance of Lynch patients, in particular to improve the detection of flat lesions that are easily missed. However, it must be taken into account that due to small sample size and the exploratory design, the results of the study do not allow any final conclusion. Multicentre trials with large patient numbers are needed to clarify this clinical important question.

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CONFLICT OF INTEREST

Robert Hüneburg and Jacob Nattermann received endoscopic equipment on loan by Fujifilm Germany but had no involvement in the design, recruitment, data collection, analysis or writing of the manuscript. Robert Hüneburg has received consulting fees for medical advice from CPP-FAP, One Two Therapeutics, Janssen Pharmaceuticals. Christian P. Strassburg has received speaker honoraria from Falk Pharma, Eisai, Astellas, Chiesi, MSD, and support for seminars from Gilead, Bristol-Myers Squibb, Abbvie, MSD, Norgine, Tillots Pharma, Eisai, Janssen, Falk Foundation, and consulting fees for medical advice from Fa. Schwabe, Astra Zeneca, Eisai and Astellas. All other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL

German Clinical Trials Register www.drks.de; DRKS00023157.

ORCID

Robert Hüneburg https://orcid.org/0000-0001-9957-8299
Dominik J. Kaczmarek https://orcid.org/0000-0003-0093-7832

REFERENCES

1. de la Chapelle A. The incidence of Lynch syndrome. Fam Cancer. 2005;4(3):233–7. https://doi.org/10.1007/s10689-004-5811-3
2. Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomark Prev. 2017;26(3):404–12. https://doi.org/10.1158/1055-9965.epi-16-0693
3. Dominguez-Valentin M, Sampson JR, Seppälä TT, ten Broeke SW, Plazzer J.-P, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15–25.
4. Edelstein DL, Axilbund J, Baxter M, Hylind LM, Romans K, Griffin CA, et al. Rapid development of colorectal neoplasia in patients with lynch syndrome. Clin Gastroenterol Hepatol : official Clin Pract J Am Gastroenterological Assoc. 2011;9(4):340–3. https://doi.org/10.1016/j.cgh.2010.10.033
5. Iino H, Simms L, Young J, Arnold J, Winship I, Webb S, et al. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. Gut. 2000;47(1):37–42. https://doi.org/10.1136/gut.47.1.37
6. Ahadova A, Seppälä TT, Engel C, Gallon R, Burn J, Holinski-Feder E, et al. The "unnatural" history of colorectal cancer in Lynch syndrome: lessons from colonoscopy surveillance. Int J Cancer. 2021;148(4):800–11. https://doi.org/10.1002/ijc.33224

7. Sánchez A, Roos VH, Navarro M, Pineda M, Caballol B, Moreno L, et al. Quality of colonoscopy is associated with adenoma detection and postcolonoscopy colorectal cancer prevention in lynch syndrome. Clin Gastroenterol Hepatol. 2022;20(3):611–21. e9. https://doi.org/10.1016/j.cgh.2020.11.002
8. Zhao S, Wang S, Pan P, Xia T, Chang X, Yang X, et al. Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. Gastroenterology. 2019;156(6):1661–74. e11. https://doi.org/10.1053/j.gastro.2019.01.260
9. Rondagh EJA, Gulikers S, Gómez-García EB, Vanlingen Y, Detisch Y, Winkens B, et al. Nonpolypoid colorectal neoplasms: a challenge in endoscopic surveillance of patients with Lynch syndrome. Endoscopy. 2013;45(04):257–64. https://doi.org/10.1055/s-0032-1326195
10. Weiss JM, Gupta S, Burke CA, Axell L, Chen L.-M, Chung DC, et al. NCCN Guidelines® insights: genetic/familial high-risk assessment: colorectal, version 1.2021: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2021;19(10):1122–32.
11. Repici A, Spadaccini M, Antonelli G, Correale L, Maselli R, Galtieri PA, et al. Artificial intelligence and colonoscopy experience: lessons from two randomised trials. Gut. 2022;71(4):757–65. https://doi.org/10.1136/gutjnl-2021-324471
12. Tanabe H, Moriichi K, Mizukami Y, Fujiya M, Okumura T. Artificial intelligence–assisted detection of colorectal polyps in Lynch syndrome. Gastrointest Endosc. 2022;95(6):1276–7. https://doi.org/10.1016/j.gie.2022.02.009
13. Moher D, Jones A, Lepage L, ftC G. Use of the CONSORT statement and quality of reports of randomized TrialsA comparative before-and-after evaluation. JAMA. 2001;285(15):1992–5. https://doi.org/10.1001/jama.285.15.1992
14. Liljegren A, Barker G, Elliott F, Bertario L, Bisgaard ML, Eccles D, et al. Prevalence of adenomas and hyperplastic polyps in mismatch repair mutation carriers among CAPP2 participants: report by the colorectal adenoma/carcinoma prevention programme 2. J Clin Oncol : official J Am Soc Clin Oncol. 2008;26(20):3434–9. https://doi.org/10.1200/jco.2007.13.2795
15. Goverde A, Eikenboom EL, Viskil EL, Bruno MJ, Doukas M, Dinjens WNM, et al. Yield of lynch syndrome surveillance for patients with pathogenic variants in DNA mismatch repair genes. Clin Gastroenterol Hepatol. 2020;18(5):1112–20.e1. https://doi.org/10.1016/j.cgh.2019.08.043
16. Huneburg R, Lammert F, Rabe C, Rahner N, Kahl P, Buttner R, et al. Chromocolonoscopy detects more adenomas than white light colonoscopy or narrow band imaging colonoscopy in hereditary non-polyposis colorectal cancer screening. Endoscopy. 2009;41(4):316–22. https://doi.org/10.1055/s-0028-1119628
17. de Jong AE, Hendriks YMC, Kleibeuker JH, de Boer SY, Cats A, Griffioen G, et al. Decrease in mortality in lynch syndrome families because of surveillance. Gastroenterology. 2006;130(3):665–71. https://doi.org/10.1053/j.gastro.2005.11.032
18. Vasen HFA, Abdirahman M, Brohet R, Langers AMJ, Kleibeuker JH, van Kouwen M, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with lynch syndrome. Gastroenterology. 2010;138(7):2300–6. https://doi.org/10.1053/j.gastro.2010.02.053
19. Ladabaum U, Ford JM, Martel M, Barkun AN. American gastroenterological association technical review on the diagnosis and management of lynch syndrome. Gastroenterology. 2015;149(3):783–813. e20. https://doi.org/10.1053/j.gastro.2015.07.037
20. Wang P, Berzin TM, Glissen Brown JR, Bharadwaj S, Becq A, Xiao X, et al. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. Gut. 2019;68(10):1813–9. https://doi.org/10.1136/gutjnl-2018-317500
21. Wang P, Liu X, Berzin TM, Glissen Brown JR, Liu P, Zhou C, et al. Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. The Lancet Gastroenterol Hepatol. 2020;5(4):343–51. https://doi.org/10.1016/s2468-1253(19)30411-x
22. Gong D, Wu L, Zhang J, Mu G, Shen L, Liu J, et al. Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. The Lancet Gastroenterol Hepatol. 2020;5(4):352–61. https://doi.org/10.1016/s2468-1253(19)30413-3
23. Su J.-R, Li Z, Shao X.-J, Ji C.-R, Ji R, Zhou R.-C, 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(2):415–24. e4. https://doi.org/10.1016/j.gie.2019.08.026
24. van Doorn SC, Hazewinkel Y, East JE, van Leerdam ME, Rastogi A, Pellisé M, et al. Polyp morphology: an interobserver evaluation for the Paris classification among international experts. Official J Am Coll Gastroenterol ACG. 2015;110(1):180–7. https://doi.org/10.1038/ajg.2014.326
25. Engel C, Vasen HF, Seppälä T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, et al. No difference in colorectal cancer incidence or stage at detection by colonoscopy among 3 countries with different lynch syndrome surveillance policies. Gastroenterology. 2018;155(5):1400–9.e2. https://doi.org/10.1053/j.gastro.2018.07.030
26. Bhurwal A, Rattan P, Sarkar A, Patel A, Haroon S, Gjeorgjievski M, et al. A comparison of 9-min colonoscopy withdrawal time and 6-min colonoscopy withdrawal time: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2021;36(12):3260–7. https://doi.org/10.1111/jgh.15701
27. van Leerdam ME, Roos VH, van Hooft JE, Balaguer F, Dekker E, Kaminski MF, et al. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019;51(11):1082–93. https://doi.org/10.1055/a-1016-4977
28. Hassan C, Antonelli G, Dumonceau J.-M, Regula J, Bretthauer M, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European society of gastrointestinal endoscopy (ESGE) guideline – update 2020. Endoscopy. 2020;52(08):687–700. https://doi.org/10.1055/a-1185-3109

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