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One in three adenomas could be missed by white-light colonoscopy – findings from a systematic review and meta-analysis

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Abstract

Background White light (conventional) colonoscopy (WLC) is widely used for colorectal cancer screening, diagnosis and surveillance but endoscopists may fail to detect adenomas. Our goal was to assess and synthesize overall and subgroup-specific adenoma miss rates (AMR) of WLC in daily practice.

Methods We conducted a systematic review in MEDLINE, EMBASE, Cochrane Library, and grey literature on studies evaluating diagnostic WLC accuracy in tandem studies with novel-colonoscopic technologies (NCT) in subjects undergoing screening, diagnostic or surveillance colonoscopy. Information on study design, AMR overall and specific for adenoma size, histology, location, morphology and further outcomes were extracted and reported in standardized evidence tables. Study quality was assessed using the QUADAS-2 tool. Random-effects meta-analyses and meta-regression were performed to estimate pooled estimates for AMR with 95% confidence intervals (95% CI) and to explain heterogeneity.

Results Out of 5,963 identified studies, we included sixteen studies with 4,101 individuals in our meta-analysis. One in three adenomas (34%; 95% CI: 30–38%) was missed by WLC in daily practice individuals. Subgroup analyses showed significant AMR differences by size (36%, adenomas 1–5 mm; 27%, adenomas 6–9 mm; 12%, adenomas ≥ 10 mm), histology (non-advanced: 42%, advanced: 21%), morphology (flat: 50%, polypoid: 27%), but not by location (distal: 36%, proximal: 36%).

Conclusions Based on our meta-analysis, one in three adenomas could be missed by WLC. This may significantly contribute to interval cancers. Our results should be considered in health technology assessment when interpreting sensitivity of fecal occult blood or other screening tests derived from studies using WLC as "gold standard".

Keywords Colorectal cancer, Colonoscopy, Adenoma, Miss rate, Detection rate, Screening

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Introduction

Colorectal cancer (CRC) is one of the leading cancers worldwide, representing almost 10% of the global cancer incidence [1] and causing an estimated 930,000 deaths worldwide in 2020 [2]. Up to 90% of CRCs likely originate from preexisting adenomatous polyps (adenomas) [3]. Early detection and removal of these precancerous lesions have proven to be effective in the reduction of incidence and mortality of CRC [4].

Colonoscopy is currently considered the "gold standard" for detecting adenomas. Any adenomas detected can be removed during the procedure, but adenomas can also be missed, potentially leading to interval cancers. Factors that may influence the adenoma miss rate (AMR) include: (1) adenoma location (e.g., behind colonic folds, at internal curves, or in the right (proximal) colon); (2) morphology (e.g., depressed, flat, pedunculated); (3) inadequate bowel preparation; (4) inadequate insertion or withdrawal technique; and (5) physician experience [4].

To reduce the AMR of conventional white-light colonoscopy (WLC), novel colonoscopic technologies (NCT) have been developed including behind-folds visualizing colonoscopic technologies (BF-CT), image-enhancement colonoscopic technologies (IE-CT), and computer-aided detection (CADe). BF-CT methods, such as the EndoRings™ system, enhance visualization by flattening or retracting mucosal folds to detect hidden polyps [5]. IE-CT, such as narrow-band imaging (NBI), improves mucosal contrast using specific light wavelengths to better identify abnormal tissue [6]. CADe systems, such as GI Genius™, use AI algorithms to identify and flag potential polyps in real time during colonoscopy [7]. Although some of these technologies have demonstrated improved diagnostic accuracy, they have not replaced WLC in daily practice [8]. The slow adoption could be explained by increased costs, the need for training to use the new technology, and a relative lack of evidence. While WLC remains the cornerstone of screening, an accurate estimation of AMR remains especially important.

The AMR of WLC is also needed to adequately interpret the accuracy of other CRC screening technologies (e.g., stool tests) derived from studies that use WLC as the reference ("gold standard") [9]. Moreover, the AMR and sensitivity of screening technologies are important input parameters in decision-analytic modeling studies on effectiveness and cost-effectiveness for CRC screening programs to inform clinical guidelines and national reimbursement recommendations [10–12].

Previously published reviews have highlighted the problem of miss rates with colonoscopy. However, previous studies have methodological shortcomings. For example, previous studies included second-look WLC, compared WLC and adjusted WLC, included studies without specified indication and non-randomized studies [9, 13]. Second-look WLC is not always conducted as a tandem colonoscopy and may include follow-up colonoscopy conducted at a later date after initial screening, accounting for variations over time, reevaluating specific regions, or performing a second-look WLC with specific interventions (e.g., changed body position or enhanced bowel preparation). Comparing WLC and adjusted WLC and including, for example, results from forward view and retroflexed view [9, 14] may introduce bias since the areas visualized in the retroflexed view differ and do not represent daily practice. For example, Zhao et al. [13] also included studies that compared auto-fluorescence imaging versus high-resolution white light [15], which do not represent daily clinical practice or a study focusing on high-risk populations [16]. In addition, the published reviews did not obtain AMRs specific for clinical characteristics such as histology, morphology or location of adenomas [17], and no information was reported on further relevant outcomes such as adenoma detection rate, patient miss rate, and surveillance interval change rate [18]. Shao et al. assessed AMR by AI-assisted technology only [19]. Therefore, we conducted a systematic review and meta-analysis of tandem colonoscopy studies comparing white light colonoscopy and NCT to assess the overall and subgroup-specific AMR and further outcomes of WLC in individuals undergoing daily practice colonoscopy including screening, diagnostic, and surveillance colonoscopy. We planned subgroup analyses for adenoma size, histology, morphology, and location.

Methods

Study eligibility criteria

Studies were included that reported the diagnostic accuracy of WLC for CRC in individuals undergoing daily practice colonoscopy (i.e., considering a mix of interventions) and applied all of the following study design features: (1) prospective same-day tandem colonoscopy studies with randomization (i.e., participants receive two same-day colonoscopies); (2) comparative trials of WLC with NCT; (3) cross-over design (i.e., crossing over from WLC to NCT or vice versa); and (4) tandem studies with polyp removal at either both procedures (tandem study type I) or only during the second procedure (tandem study type II). No restrictions on publication year were applied and only studies published in English were included.

Excluded studies were: (1) non-randomized studies; (2) studies comparing different WLC variants (e.g., different withdrawal times) or different NCTs; (3) studies without a proper cross-over design (i.e., one NCT-WLC study arm and in the other arm individuals receiving WLC twice; 4) studies focusing only on one indication for colonoscopy (either screening, diagnostic work-up or

surveillance) or indications for colonoscopy not reported; and 5) reviews, case reports or studies performed in animals or in vitro colon models.

Information sources

A comprehensive systematic literature search was performed in three electronic databases (Medline via PubMed, EMBASE via Ovid, and Cochrane Library). The full search code is reported in the Appendix.

We also manually searched the reference lists of all articles included in the systematic review. The last search was performed in July 2023. If reported study data were incomplete or there was uncertainty about extracted data, we requested additional information from the authors by email. For three of the included studies, detailed information on AMRs (without classifying sessile serrated polyps as adenomas as in the original studies) or additional information not presented in the original studies was extracted from the study by Brand and colleagues [20], which pooled these three studies.

Data collection and extraction process

Two independent reviewers (MB, MS, IK, JK) systematically extracted all data using standardized forms designed prior to the study. Any disagreement was resolved by a third reviewer (BJ). Extracted information included: (1) number of detected adenomas; (2) main study characteristics including study type, intervention and individual and adenoma characteristics; (3) colonoscopy setting and bowel preparation (indication for colonoscopy, quality of bowel preparation); and (4) further characteristics of devices and procedures.

Data items, outcome definitions and summary measures

The primary outcome of our study is the overall AMR of WLC. Secondary outcomes are AMRs stratified by subgroups including size (1–5 mm, 6–9 mm, and ≥ 10 mm diameter according to the colonoscopy report), histology (advanced vs. non-advanced adenomas), morphology (polypoid vs. flat adenomas), anatomical location (proximal colon vs. distal colon or rectal adenomas). Further secondary outcomes are: (1) adenoma detection rate (ADR) representing the proportion of individuals with at least one adenoma detected among all individuals; (2) patient miss rate (PtMR) representing the proportion of individuals with no adenomas detected during colonoscopy despite having one or more adenomas; (3) surveillance interval change rate (SICR) representing the proportion of individuals who would be recommended to change their surveillance interval after the second examination (NCT) in comparison to the first examination (WLC) applying the guidelines of the European Society of Gastroenterology (ESGE) [21, 22], European Union (EU) [23], or United States Multi-Society Task Force on Colorectal Cancer (MSTF); [24, 25] and (4) the rate of complete colonoscopic examination reaching the cecum (CIR). CIR of WLC and NCT from both study arms were combined because they served as a quality indicator of the studies.

In particular, AMR was defined as the proportion of detected adenomas in the second examination relative to the total number of adenomas detected in both examinations in the WLC-NCT arm with the exception of tandem study type II where the second examination was conducted by a second endoscopist blinded to the results of the first examination [26]. In this tandem study type II, AMR was defined as the proportion of adenomas missed by WLC in both study arms (WLC-NCT, NCT-WLC) relative to the number of adenomas detected by either WLC or NCT in both study arms (WLC-NCT and NCT-WLC).

Similarly, ADR and PtMR were defined based on individuals with one or more adenomas and individuals falsely classified as healthy (see glossary in the Appendix for further definitions).

As advanced adenomas, we classified adenomas ≥ 10 mm in size or with villous histology or high-grade dysplasia. Adenomas detected in the cecum, the ascending colon, the hepatic flexure, or the transverse colon were considered proximal adenomas, whereas adenomas detected in the splenic flexure, the descending colon or the rectum were considered distal adenomas [27].

Quality assessment of included studies

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [28, 29] was utilized to assess study quality of the included studies in the four domains: patient selection, index test characteristics, reference standard characteristics, and flow and timing. Applicability of the primary studies is assessed for the first three domains [28].

Synthesis of results and statistical analysis

As we expected heterogeneity due to study characteristics and technologies applied, random-effects meta-analyses were applied to combine primary and secondary outcomes of WLC, that is total AMRs, AMRs in subgroups, PtMRs, ADRs, CIRs, and SICRs. We used generalized linear mixed-effects models (GLMM) suggested by Hamza et al., Stijnen et al., [30, 31] in which the normal within-study likelihoods are replaced by the binomial likelihoods. We used GLMMs with a binomial-normal model for pooling single proportions, and GLMMs with a hypergeometric-normal model for pooling odds ratios (OR) comparing the outcomes between WLC and NCT. For the pooled AMR

(p-AMR) and other pooled proportions, the 95% confidence interval (95% CI) was based on the Wilson score method; for the pooled CIR (p-CIR) the 95% confidence interval (95% CI) was based on the Clopper-Pearson method to account for extreme proportions.

Heterogeneity of the outcomes was assessed by the likelihood ratio test (LRT). A p-value of <0.1 was considered statistically significant for the LRT. The I^2 statistic was used to quantify the heterogeneity across studies [18]. I^2 values of 25%, 50%, and 75% are considered low, moderate, and high. In addition, between-studies variance τ^2 was estimated.

A random-effects meta-regression was conducted to investigate the sources of heterogeneity and the effect of study features and adenoma characteristics on miss rates. The study characteristics covariates were first tested in univariate regression models, and thereafter used in the multivariate meta-regression model in a stepwise backward selection process ($p<0.05$). For each characteristic, the proportion of explained between-study variance (τ^2) was determined.

Sensitivity analyses for p-AMR were performed on tandem study type by excluding tandem type II studies. Tandem type II studies, where adenomas are removed only after the second intervention, eliminate the risk of observer bias, but they are also performed less often. In addition, a sensitivity analysis was conducted on adenoma location because of existing evidence about differences in performance of coloscopy technologies. We excluded studies where only the right colon was examined, as the right colon is assumed to be associated with higher miss and interval cancer rates.

The Jonckheere-Terpstra test was applied to test for trends for p-AMR in subgroups with different adenoma sizes.

Results of the meta-analyses are presented as forest plots created with the meta package, version 7.0–0 [32], and the metaphor package, version 4.6–0 [33] for R statistics software, version 4.4.0 (April 24, 2024) (R Foundation for Statistical Computing, Vienna). The results of this study are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [34]. The study was registered at the Research Committee for Scientific Ethical Questions (RCSEQ) of UMIT TIROL – University for Health Sciences and Health Technology, Hall in Tirol, Austria (registration # 2283).

Role of the funding source

The study was funded by the Main Association of Austrian Social Security Institutions. The funding body had no influence on the design of the study, collection, analysis, and interpretation of data or the writing of the manuscript.

Results

Study selection

Our systematic search identified 5,963 records (see Appendix Fig. 1). No further articles were detected by the manual search through the reference lists. After removal of 1,252 duplicates and screening titles and abstracts, 75 articles were assessed in full text. Among these, sixteen studies met the inclusion criteria and were included in our systematic review and meta-analyses.

Study characteristics

The main characteristics of studies included in our systematic review are summarized in Table 1. In eight studies WLC was compared to behind-folds visualizing colonoscopic technologies (BF-CT); in four studies WLC was compared to image-enhancement colonoscopic technologies (IE-CT); and in another four studies WLC was compared to computer-aided detection colonoscopic technologies (CADe). Our primary analysis is based on data from 4,101 randomized individuals. The number of randomized individuals per study ranged from 41 [35] to 813 [17]. The study arms providing data for our analysis included a total of 1,977 individuals. In these study arms, the median or mean age ranged from 46 to 65 years and the average number of adenomas ranged from 0.56 [36] to 2.77 [37]. The entire colon was inspected in fourteen studies [5, 26, 35–46], whereas in two studies [17, 47] only the proximal colon was examined.

In fourteen tandem studies, polyps were removed immediately (type I) and both examinations were performed by the same endoscopist. In the studies of De Palma et al. [42] and Min et al., [26] adenomas were removed only in the second examination (type II); however, in Min et al., [26] the second procedure was performed by another endoscopist blinded to the results of the first procedure. Only one study was based on results from a single endoscopist [47], whereas all other studies involved multiple endoscopists (up to 32) [44].

Information on the colonoscopy indication and the quality of bowel preparation is displayed in Table 2. The number of included individuals with screening, diagnostic work-up, and surveillance indications in each study arm ranged from 17 to 94%, 2–63%, and 3–72%, respectively. Only one study included individuals referred for adenoma removal in addition to the other indications [40].

Further information on colonoscopy devices and procedures, endoscopist characteristics and features of the studies are provided in the Appendix Table 1. The exclusion criteria for individuals are also reported in Appendix Table 2. In thirteen studies individuals were excluded from the study after randomization for reasons including inadequate bowel preparation, failure to reach the cecum, and technical failures. In thirteen studies, a per-protocol

Table 1 Main characteristics of studies included in the systematic review and meta-analysis

	Matsuda 2008 [47]	Hewett 2010 [37]	Leufkens 2011 [38]	Ikematsu 2012 [17]	Gralnek 2014 [36]	Dik 2015 [5]	Halpern 2015 [39]	Min 2017 [26]	Papanikolaou 2017 [40]	Triantafyllou 2017 [41]	De Palma 2018 [42]	Riu Pons 2020 [35]	Wang 2020 [43]	Kamba 2021 [44]	Glissen Brown 2022 [45]	Wallace 2022 [46]
Country	J	USA	USA, NL, I, B, UK	J	NL, USA, IL	NL, USA, IL	IL, D	China	GR	GR	I	Spain	China	J	USA	I, UK, USA
Type of NCT	IE-CT	BF-CT	BF-CT	IE-CT	BF-CT	BF-CT	BF-CT	IE-CT	BF-CT	BF-CT	BF-CT	IE-CT	CADe	CADe	CADe	CADe
Total randomized, n	167	100	448	813	197	126	126	152	220	200	288	41	382	358	234	249
NCT-WLC randomized, n	83	52	226	406	101	62	66	77	110	100	144	21	192	179	116	116
NCT-WLC included, n	83	52	176	389	97	57	52	71	107	100	137	21	184	171	113	109
WLC-NCT randomized, n	84	48	222	407	96	64	60	75	110	100	144	20	190	179	116	114
WLC-NCT included, n	84	48	173	393	88	59	54	70	108	100	137	20	185	173	110	104
Age NCT-WLC	62 ± 10[a]	61 (1)[b]	58 (23–79)[C]	63 (10)[b]	57 (21–70)[c]	58 ± 9[a]	58 ± 8[a]	46 ± 13[c]	62 (10)[b]	61 (10)[b]	55 ± 13[a]	60[d]	48 ± 10.82[a]	61 ± 9.89[a]	61 ± 9.83[a]	63 ± 8.2[a]
Age WLC-NCT	62 ± 9.5[a]	63 (1.2)[b]	57 (26–83)[c]	63 (9.9)[b]	56 (22–70)[c]	60 ± 9.3[a]	55 ± 7.9[a]	48 ± 13.1[c]	64 (9.5)[b]	61 (9.6)[b]	56 ± 12.3[a]	59[d]	47 ± 10.38[a]	61 ± 10.01[a]	61 ± 8.45[a]	65 ± 8.1[a]
Females NCT-WLC, n (%)	25 (30)	24 (46)	54 (31)	122 (31)	55 (57)	16 (28)	31 (60)	34 (48)	61 (56)	46 (46)	66 (48)	8 (39)	91 (49)	42 (24)	59 (52)	36 (31)
Females WLC-NCT, n (%)	35 (42)	19 (40)	63 (36)	116 (30)	46 (52)	29 (49)	29 (54)	32 (46)	58 (52)	48 (48)	65 (47)	11 (55)	99 (54)	41 (23)	42 (38)	37 (32)
Ø adenoma. NCT- WLC	0.80	2.02	0.77	1.00	0.61	1.18	0.77	NR	0.68	1.09	0.64	1.57	0.78	1.42	1.50	2.12
Ø adenoma. WLC-NCT	1.13	2.77	0.86	1.09	0.56	0.98	0.70	NR	0.74	0.86	0.74	1.20	0.65	1.25	1.31	2.17
Colon examined	RC	WC	WC	RC	WC	WC	WC	WC	WC	WC	WC	WC	WC	WC	WC	WC
Setting	NR	A	A, non A	A	A, non A	A, non A	A, non A	A, non A	A, non A	A, non A	A	non A	non A	A, non A	A	A, non A
Single/multi center	Single	Single	Multi	Multi	Multi	Multi	Multi	Multi	Multi	Multi	Single	Single	Single	Multi	Multi	Multi
Type tandem study	Type I	Type I	Type I	Type I	Type I	Type I	Type I	Type II	Type I	Type I	Type II	Type I	Type I	Type I	Type I	Type I
Endoscopists, n	1	2	15	27	15	6	> 1	> 1	5	6	4	5	3	32	> 1	> 1
Diff. endoscopist 2nd	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Endoscopist blinded alloc.	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes

Legend: Ø adenoma. – average number of adenomas detected per study group, A – academic, alloc. – allocation, B – Belgium, BF-CT – behind-folds visualizing colonoscopic technologies, diff. – different, CADe – computer aided diagnosis endoscopy, GR – Grece, I – Italy, IE-CT – image-enhancement colonoscopic technologies, IL – Israel, J – Japan, NCT – novel colonoscopic technologies, NR – not reported, NL – Netherlands, RC – right colon, UK – United Kingdom, USA – United States of America, WC – whole colon, WLC – white light colonoscopy. (a) indicates standard deviation, (b) indicates standard error, (c) indicates range, (d) indicates that no measure of variability is available

analysis was performed, and an intention-to-treat analysis was conducted in Leufkens et al. [38]

Risk of bias and applicability

The summary of the methodological quality assessment (QUADAS) of the synthesized studies is presented in the Appendix Table 4 and Appendix Fig. 2. The quality assessment showed a high risk of bias in the domains 'reference standard' and 'flow and timing' because in almost all studies — with the exception of Min et al., [26] — endoscopist performed both examinations, and the exclusion of individuals after randomization and per-protocol analyses (e.g., due to poor bowel preparation) [5, 17, 26, 35, 36, 38–40, 42].

Pooled results from meta-analyses

The overall AMR from sixteen studies (including 2,248 adenomas) included in our systematic review ranged from 0.15 (95% CI: 0.10–0.21) [26] to 0.48 (95% CI: 0.36–0.61%) [5] (see Fig. 1). The pooled overall AMR (p-AMR) was 0.34 (95% CI: 0.30–0.38). The I^2 statistic (71%, heterogeneity test $p < 0.01$) indicated strong heterogeneity. The between-study variance τ^2 was 0.1004.

Subgroup analyses for AMR

Figure 2 summarizes the results for all subgroup analyses. The size-specific AMRs were reported in eight studies including 1,203 adenomas [5, 17, 37–39, 42, 46]. AMR significantly decreased with increasing adenoma size, as demonstrated by the test for trend describing overall correlation between adenoma size and AMR ($p < 0.001$). Pooled AMRs are 0.36 (95% CI: 0.33–0.40) for size 1–5 mm, 0.27 (95% CI: 0.20–0.36) for size 6–9 mm, and 0.12 (95% CI: 0.07–0.20) for size ≥ 10 mm.

AMR for advanced and non-advanced adenomas was reported in nine studies including 1,238 adenomas. In non-advanced adenomas, the pooled AMR was 0.42 (95% CI: 0.38–0.45), which is substantially higher than in advanced adenomas (pooled AMR: 0.21, 95% CI: 0.14–0.29, $p < 0.001$).

AMRs for proximal adenomas were reported in eleven studies (1,075 adenomas), and in nine studies (388 adenomas) for the distal colon. Pooled AMRs did not differ ($p = 0.89$) between proximal (pooled AMR: 0.36, 95% CI: 0.30–0.42) and distal (pooled AMR: 0.36, 95% CI: 0.31–0.40) adenomas.

Morphology-specific AMRs were reported in six studies including 1,118 individuals. With a pooled AMR of 0.50 (95% CI: 0.36–0.64), flat adenomas were more likely to be missed than polypoid adenomas (pooled AMR: 0.27, 95% CI: 0.20–0.36, $p < 0.01$).

In a subgroup analysis, pooled AMRs differ between studies with IE-CT, BF-CT and CADe (for more details, see Appendix Fig. 20).

Heterogeneity analysis

Univariate meta-regression analysis assessing the impact of study characteristics on p-AMR showed tandem study type as a significant factor, explaining about half of the between-study variance ($\tau^2 = 0.0333$, $p < 0.01$). The fraction of the variation across studies due to heterogeneity, relative to chance of variation heterogeneity I^2, decreased from 71% (primary analysis) to 54% (studies with type I tandem design). In further subgroup analyses, for example, for adenoma size, I^2 decreased further. No further statistically significant factors explaining heterogeneity were identified in the meta-regression analysis.

Sensitivity analyses

The sensitivity analysis restricting the analysis to the fourteen studies examining the entire colon (1,724 adenomas) yielded a pooled AMR of 0.34 (95% CI: 0.29–0.38). The sensitivity analysis combining the fourteen tandem type I studies yielded a pooled AMR of 0.36 (95% CI: 0.32–0.39). The 95% CIs of both sensitivity analyses covered the base-case result of 0.34.

Secondary outcomes

The pooled ADR (1,638 individuals) is 0.37 (95% CI: 0.29–0.46), and the pooled PtMR (389 individuals) is 0.18 (95% CI: 0.14–0.23).

The pooled CIR, combining individuals in the WLC and NCT arms, is 0.99, and the pooled SICR of WLC ranges from 0.04 to 0.08 depending on the applied guideline (Table 3; for more details, see Appendix Figs. 15, 16 and 17).

Discussion

This systematic review with meta-analyses combines data from sixteen tandem studies, including a total of 4,101 individuals. We found that about one in three adenomas (0.34; 95% CI: 0.30–0.38) could be missed by WLC in individuals undergoing screening, diagnostic, or surveillance colonoscopy. The subgroup analysis for adenoma characteristics showed that AMRs significantly increased with smaller size, non-advanced stage, and flat morphology of adenomas. Adenoma locations did not influence AMR.

In contrast to our results, van Rijn and colleagues reported an overall p-AMR of 0.22 (95% CI: 0.19–0.26) [9], and size-specific p-AMRs of 0.26 (95% CI: 0.27–0.35) for 1–5 mm adenomas, 0.12 (95% CI: 0.08–0.18) for 6–9 mm adenomas and 0.02 (95% CI: 0.003–0.07) for ≥ 10 mm adenomas. The results of van Rijn et al. are based on a meta-analysis of six cohorts, including a total of 465 individuals, that combined data of the different intervention arms (e.g., including NCT). In or meta-analysis, the focus was specifically on the miss rates of WLC.

Table 2 Colonoscopy intervention setting and bowel preparation of the studies included in the systematic review and meta-analysis

	Matsuda 2008[47]	Hewett 2010 [37]	Leufkens 2011 [38]	Ikematsu 2012 [17]	Gralnek 2014 [36]	Dik 2015 [5]	Halpern 2015 [39]	Min 2017 [26]	Papanikolaou 2017 [40]	Triantafyllou 2017 [41]	De Palma 2018 [42]	Riu Pons 2020 [35]	Wang 2020 [43]	Kamba 2021 [44]	Glissen Brown 2022 [45]	Wallace 2022 [46]
Indication NCT-WLC												NR[a]				
Screening, n (%)	35 (42)	19 (37)	86 (49)	88 (23)	50 (52)	17 (30)	49 (94)	30 (42)	76 (69)	63 (63)	32 (23)		58 (32)	31 (17)	68 (60)	41 (35)
Surveillance, n (%)	42 (51)	31 (60)	51 (29)	280 (72)	20 (21)	21 (37)	2 (4)	15 (21)	76 (69)	23 (23)	57 (42)		19 (10)	59 (33)	45 (40)	75 (65)
Diagnostic workup	6 (7)		38 (22)	21 (5)	27 (28)	19 (33)	1 (2)	41 (58)	29 (26)	14 (14)	48 (35)		107 (58)	88 (50)		
Family history of CRC				0 (0)												
Polypectomy									5 (5)							
Other		2 (4)														
Indication WLC-NCT												NR[a]				
Screening, n (%)	41 (49)	13 (27)	91 (53)	95 (24)	53 (60)	17 (29)	46 (85)	33 (47)	74* (67)	59 (59)	29 (21)		55 (30)	31 (18)	65 (59)	41 (36)
Surveillance, n (%)	36 (43)	31 (65)	36 (21)	273 (69)	16 (18)	19 (32)	1 (3)	16 (23)		28 (28)	62 (45)		13 (7)	69 (38)	45 (41)	73 (64)
Diagnostic workup	7 (8)		44 (26)	24 (6)	19 (22)	23 (39)	7 (13)	38 (54)	33 (30)	13 (13)	46 (34)		117 (63)	78 (44)		
Family history of CRC				1 (0.3)												
Polypectomy									3 (3)							
Other		4 (8)														
Bowel preparation NCT-WLC												NR[a]				
Excellent, n (%), good, n (%), fair, n (%)	18 (22), 49 (59), 16 (19)	15 (29), 34 (64), 3 (6)		115 (30), 219 (56), 55 (14)												
Ottawa scale			4 (3–5)		3.0 (0.0–5.5)											
Aronchick scale, 1–3, n (%), 4–5, n (%)														169 (98), 4 (2)		
BBPS score						7.8 ± 1.1[b]	3.4 ± 1.7[b]	8.0 (1.0)[c]	9.0 (8.0–9.0)[c]	9.0 (3.0–9.0)[d]	7.1 ± 1.1[b]		7.2 ± 1.4[b]		9 (8–9)[c]	8.0 ± 1.5[b]
Bowel preparation WLC-NCT												NR[a]				
Excellent, n (%), good, n (%), fair, n (%)	23 (27), 49 (58), 12 (14)	14 (29), 34 (71), 0 (0)		131 (33), 220 (56), 42 (11)												
Ottawa scale			4 (3–5)		3 (1.3–5.8)											

Table 2 (continued)

	Matsuda 2008[47]	Hewett 2010 [37]	Leufkens 2011 [38]	Ikemat-su 2012 [17]	Gral-nek 2014 [36]	Dik 2015 [5]	Halpern 2015 [39]	Min 2017 [26]	Papan-ikolaou 2017 [40]	Trian-tafyllou 2017 [41]	De Palma 2018 [42]	Riu Pons 2020 [35]	Wang 2020 [43]	Kamba 2021 [44]	Glissen Brown 2022 [45]	Wallace 2022 [46]
Aronchick scale, 1–3, n (%), 4–5, n (%)														166 (97), 5 (2.9)		
BBPS score						7.8 ± 1.1[b]	3.2 ± 1.8[b]	8.0 (1.0)[c]	9.0 (8.0–9.0)[c]	9.0 (5.0–9.0)[d]	7.2 ± 1.0[b]		7.1 ± 1.4[b]		9 (8–9)[c]	8.0 ± 1.3[b]

Legend: * summary of screening and surveillance individuals, BBPS – Boston Bowel Preparation Scale, CRC – colorectal cancer, NCT – novel colonoscopic technologies, NR – not reported, WLC – white light colonoscopy. (a) indicates that data was not reported for the two arms of the study, only overall sample information was provided. (b) indicates standard deviation, (c) indicates inter-quartile range, (d) indicates range

Although AMRs decreased with adenoma size, the still considerably high miss rate of large adenomas could be a serious issue in clinical practice because of specific characteristics of these adenomas. In particular, the risk of having advanced features (such as villous histology or high-grade dysplasia) or developing into metachronous cancer (i.e., cancer diagnosed at least 6 months after the index procedure) is much higher in large adenomas (20 – 30%) compared to small adenomas (7 – 12%) [48–50]. Our results also suggest that 1–5 mm and 6–9 mm adenomas are overlooked more frequently than large adenomas, which is an important finding considering that T1 carcinoma may be found in a considerable portion in lesions < 9 mm in diameter [51]. This result is in line with the meta-analysis of van Rijn et al. [9]

A recent meta-analysis comparing WLC and NCT showed that the overall AMR was lower for NCT compared with WLC (OR: 0.19; 95% CI: 0.14–0.26; $p < 0.01$). However, the authors could not show a significant improvement with NCT for the detection of adenomas < 10 mm [52].

Our study did not confirm a significant influence of adenoma location on AMRs. Previous studies provided evidence for lower performance of WLC in the proximal colon compared to the distal colon [53, 54]. One reason for the contradicting results may be that the NCTs included in our operationalized gold standard have similar performance differences across locations as WLC. Another reason could be a lack of sufficient sample size for the localization subgroups in our meta-analysis. This, however, seems unlikely given the exact same pooled AMRs (i.e., 0.36) for proximal and distal adenomas. Our study confirms the findings of previous studies that flat adenomas are missed significantly more frequently by WLC than polypoid adenomas [55]. Flat adenomas are of greater clinical significance due to their distinct neoplastic potential [56–58]. Flat adenomas often harbor serrated histology, which is responsible for 20–30% of interval cancers. Furthermore, serrated lesions are mostly present in the proximal colon and may be often overlooked due to insufficient bowel preparation [59, 60].

We estimated a pooled ADR of 0.37 (95% CI: 0.29–0.46). ADR is a population-specific benchmark for the quality of colonoscopy [61], influenced by prevalence, sex, age, bowel preparation quality, risk factors, and skills of endoscopist [62, 63]. ADR should be at least approximately 25% in men, 15% in women and 15–20% for screening colonoscopy, but no universal threshold can be defined [64–66]. The relatively high pooled ADR in our study could be explained by the expertise of the endoscopists and the inclusion of individuals undergoing additional surveillance and diagnostic colonoscopy, for which the ADR is higher [67]. Assuming that, in daily practice, endoscopists may be less experienced compared

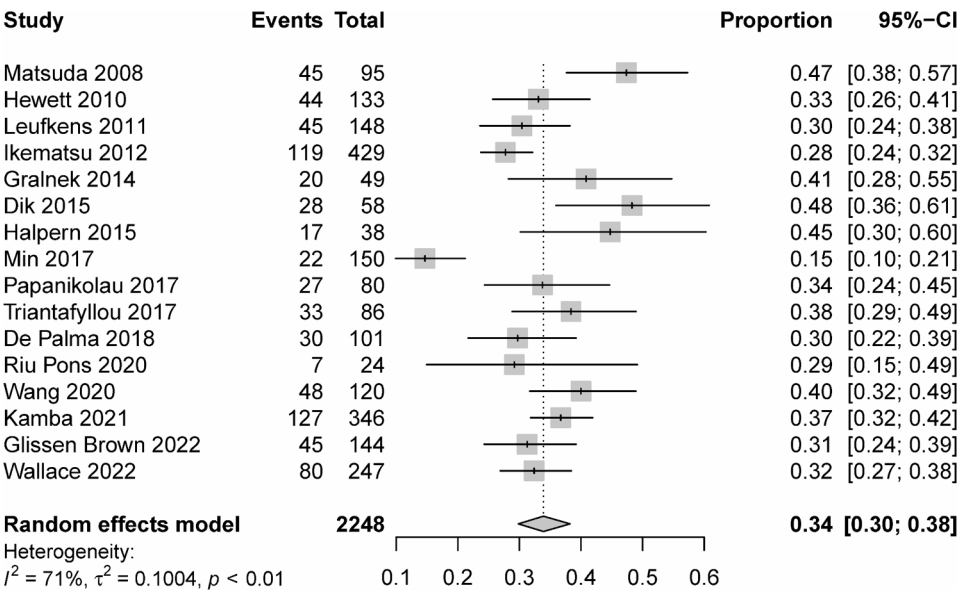

Fig. 1 Forest plot for the pooled overall adenoma miss rate of white-light colonoscopy. *Legend*. Events represent number of adenomas missed by WLC; total represents number of adenomas detected in the study arms of interest

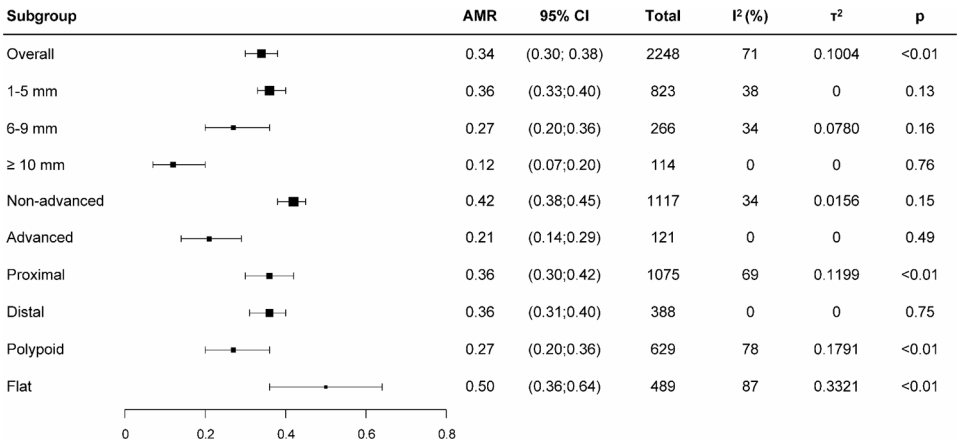

Fig. 2 Summary of subgroup for the pooled overall adenoma miss rate of white-light colonoscopy. *Legend*. AMR – adenoma miss rate. Total represents the number of adenomas detected the study arms of interest

Table 3 Summary of pooled ADR, PtMR, CIR and SIRC of WLC

Pooled parameter	Value	95% CI	Total individuals	I^2 (%)	τ^2	*p*
p-ADR of WLC	0.37	0.29–0.46	1,638	90	0.3490	< 0.01
p-PtMR of WLC	0.18	0.14–0.23	389	14	0.0254	0.32
p-CIR (combined for WLC and NCT)	0.99	0.98–0.99	4,106	72	0.7724	< 0.01
p-SICR of WLC according to MSTF guidelines	0.08	0.04–0.17	542	87	0.6803	< 0.01
p-SICR of WLC according to ESGE guidelines	0.04	0.03–0.07	524	0	0	0.80
p-SICR of WLC according to EU guidelines	0.06	0.04–0.08	661	0	0	0.85

ESGE – European Society of Gastroenterology, EU – European Union, MSTF – United States Multi Society Task Force on Colorectal Cancer, p-ADR – pooled adenoma detection rate, p-CIR – pooled cecal intubation rate, p-PtMR – pooled patient miss rate, p-SICR – pooled surveillance interval change rate, WLC – white light colonoscopy

to those in our included studies, the AMR of daily practice colonoscopy may be even higher than in or meta-analysis. However, we excluded pure screening studies with smaller prevalence of adenomas that also tend to exclude patients with complicated anatomy, imperfect bowel preparation, bleeding, or abnormal imaging results which may not be representative of daily practice. The adenomas missed by WLC and later detected by a

second-look NCT led to a shortening of the surveillance interval, according to the international guidelines [21, 23, 24] in 4% (ESGE guidelines, five studies) to 8% (MSTF, five studies) of the individuals.

The pooled CIR of 99% in our meta-analysis reflects the controlled study setting, whereas population-based studies study have reported a CIR of only 87% in daily practice [68].

To our knowledge, this is the first meta-analysis of AMR of WLC determined through tandem colonoscopy studies exclusively comparing WLC with NCT. NCTs are being developed to improve detection rates of WLC, for example, for adenomas hidden behind colonic folds and flexures, as well as for flat lesions. Studies in which WLC was performed twice were purposefully excluded because AMR would mainly reflect the expertise of the endoscopists or the impact of different techniques, including changes of the position of the individual, or withdrawal times [13].

Another strength of our study is that it reflects daily practice colonoscopy, including colonoscopy for screening, diagnostic work-up, and surveillance. In our meta-regressions, including indications as a predictor of AMR, provided no evidence for differences between indications. However, simple calculations based on the statistically non-significant odds ratios in the meta-regression are consistent with a 10% increased AMR in screening individuals compared to the overall AMR. This result highlights the need for further investigations in screening settings to get statistically reliable estimates.

The pooled results most likely reflect lower boundaries of daily clinical practice, as the included studies have been conducted in a controlled setting with colonoscopy performed by experienced endoscopists, likely under less time-pressure. Additionally, another clinical study presented an analysis suggesting that a significantly higher ADR with NCT is only observed among endoscopists who have a median ADR in WLC below 60% [69].

Our meta-analysis has several limitations. In 93.75% of the included studies, the same endoscopist performed both examinations and was therefore aware of results of the first test. This could introduce bias in two directions: for example, an AMR underestimation due to the one-and-done effect, or an AMR overestimation due to the second-look effect. However, having a second endoscopist perform the second colonoscopy reduces efficiency and power due to diverse characteristics of the endoscopists. In addition, it was not possible to blind the colonoscopists to the technology being used (WLC, NCT), which may have induced an unintentional bias towards one of the two technologies. Standard-definition colonoscopy and high-definition colonoscopy were summarized under WLC to reflect diversity in clinical practice, even though high definition endoscopy is becoming widespread [70, 71]. However, there is evidence that differences between those technologies are marginal for the detection of colonic adenomas [72]. Currently, there is no true "gold standard" for adenoma detection. Tandem studies are considered the most reliable study designs [9], yet they can still lead to underestimation of AMR in WLC because of adenomas missed by NCT. It is unlikely that adenomas are missed independently by both technologies. However, due to the risk of underestimating the AMR of WLC due to the still imperfect reference standard of NCT, a high risk of bias in the QUADAS-2 domain 'reference standard' was identified. Most of the included studies were type I tandem studies with polyp removal during both procedures, but endoscopists were mostly blinded to the results of the first procedure. In type II studies, a second endoscopist is always blinded to the prior examination results. The type II study design allows for a clearer separation between the performance of the first and the second endoscopist and between the applied technologies. However, only two studies in our review applied a type II study design. Most of the studies were powered only for the primary outcome, overall AMR, and are underpowered for the secondary outcomes, with small samples leading to large confidence intervals. One limitation of all meta-regressions is the potential presence of unmeasured characteristics that might explain heterogeneity. However, we covered a broad selection of study characteristics as covariates in our meta-regressions, and our sensitivity analyses on measured characteristics demonstrated the robustness of our results. Finally, our quality assessment of the included studies applying QUADAS-2 is limited, as it is not entirely adequate for studies with crossover design, but to our knowledge, there are no alternatives [28]. Information on the ADR of colonoscopists, an important quality indicator, was not reported by every study. There is recent evidence, that improved ADR over time is associated with lower CRC risk in patients who underwent colonoscopy [73].

Missed adenomas during colonoscopy are responsible for up to 50% of interval cancers [48]. According to our findings, the AMR of WLC is considerably higher than previously estimated [9]. In particular, for evaluations of screening programs applying decision-analytic modeling, our findings should be considered to test robustness of model results based on lower miss rates. Our findings may potentially impact modelling-based recommendations on optimal screening intervals for CRC screening programs. However, the reasons for missed adenomas beyond size require further investigations.

Further meta-analysis of upcoming tandem studies should evaluate the AMR of WLC as determined by specific types of NCT and potentially focus on specific indications. We suggest that future accuracy studies report subgroup-specific results for such variables. As stated by

the included studies, handling of hardware NCT devices was more difficult due to their cumbersome nature. Therefore, manufacturers have made efforts to counteract this issue, for example, by increasing the flexibility of colonoscopes. As better evidence on specific NCT versions becomes available, future meta-analyses can also support comparisons of the new technologies and WLC to support the implementation of improved colonoscopic technologies in clinical practice. Updated recommendations of the American Gastroenterological Association integrating AI into clinical practice are expected in 2025.

For a full assessment of different colonoscopy technologies or algorithms, it is important to assess the comparative long-term benefits, harms and costs in a full health technology assessment as well as the tradeoffs between sensitivity and specificity, the related benefit-harm balance [74] and the incremental cost-effectiveness ratios [12]. These assessments are often performed using decision-analytic modeling [12] joining test accuracy, treatment effectiveness and long-term morbidity and mortality of colorectal cancer [12, 75]. Our results provide the input parameters for such decision analyses and health technology assessments and should inform the specification of clinical guidelines regarding this topic. Guidance for the health technology assessments of AI supported technologies are currently being developed [76, 77].

Conclusion

Our meta-analysis of tandem colonoscopy studies comparing white light colonoscopy (WLC) to novel colonoscopic technologies (NCT) suggests that one in three adenomas could be missed by WLC in individuals undergoing daily practice colonoscopy. Our study confirms a significantly higher adenoma miss rate for smaller, non-advanced and flat adenomas. We believe that our pooled ADRs may be an underestimate, as NCT is an imperfect and not completely independent reference technology for WLC. Our results should be considered in health technology assessment when interpreting the sensitivity of fecal occult blood or other screening tests that rely on WLC as the "gold standard". Finally, we recommend further evidence synthesis on novel-colonoscopic technologies, as our subgroup analysis indicate substantial improvements in AMR with NCTs. A full health technology assessment on NCTs could support implementation decisions and practice guidelines based on long term benefit-harm and cost-effectiveness outcomes.

Abbreviations

ADR	Adenoma detection rate, percentage of individuals with at least one adenoma detected
AFI	Autofluorescence imaging videoendoscopy
AMR	Adenoma miss rate
B	Belgium
BBPS	Boston Bowel Preparation Scale
CADe	Computer-aided detection
CI	Confidence interval
CIR	Cecal intubation rate
CRC	Colorectal cancer
CTC	Computed tomography colonography
ESGE	European Society of Gastroenterology
EU	European Union
FEM	Fixed-effect model
FICE	Fujinon intelligent chromoendoscopy.
FUSE	Full spectrum endoscopy
GLMM	Generalized linear mixed-effects model
GR	Greece
I	Italy
IL	Israel
ITT	Intention-to-treat
J	Japan
LCI	Linked-color imaging
LRT	Likelihood ratio test
MSTF	United States Multi-Society Task Force on Colorectal Cancer
n	Number
NBI	Narrow-band imaging
NCT	Novel colonoscopic technologies
NL	Netherlands
NR	Not reported
OR	Odds ratio
p-ADR	Pooled adenoma detection rate
p-AMR	Pooled adenoma miss rate
p-CIR	Pooled cecal intubation rate
p-OR	Pooled odds ratio
p-PtMR	Pooled patient miss rate
p-SICR	Pooled surveillance interval change rate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PtMR	Patient miss rate
QUADAS	Quality Assessment of Diagnostic Accuracy Studies-2
RC	Right colon
RCT	Randomized control trial
REM	Random-effect model
SICR	Surveillance interval change rate
Study arm	Refers to the group of patients that received the same procedure (i.e., WLC-NCT arm received WLC first, NCT second, NCT-WLC arm received NCT first, WLC second)
Tandem study type I	Tandem study with polyp removal only during both procedures
Tandem study type II	Tandem study with polyp removal only during the second procedure
UK	United Kingdom
USA	United States of America
WC	Whole colon
WLC	White light colonoscopy

Supplementary Information

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Supplementary Material 1

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Author contributions

BJ, MB, MA, GS, DÖ, FR, MJ, MF, and US made substantial contributions to conception and design.BJ, MB, MA, MS, JT, MF, JK, JS, IK, and US made substantial contributions to acquisition of data and analysis.BJ, MB, MA, MS, JT, GS, AK, TF, ISF, DÖ, FR, JK, JS, IK, MJ, MF, and US were involved in interpretation of data and in drafting the manuscript and revising it critically for important

intellectual content.BJ, MB, MA, MS, JT, GS, AK, TF, ISF, DÖ, FR, JK, JS, IK, MJ, MF, and US agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.BJ, MB, MA, MS, JT, GS, AK, TF, ISF, DÖ, FR, JK, JS, IK, MJ, MF, and US read and approved the final manuscript. Proofreading and language editing was performed by Dr. Lyndon James (Harvard University).

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Data availability
The data used and/or analyzed during the current study are presented in the publication.

Declarations

Ethics approval and consent to participate
The study was registered at the Research Committee for Scientific Ethical Questions (RCSEQ) of UMIT TIROL – University for Health Sciences and Health Technology, Hall in Tirol, Austria (registration # 2283). Only published data are used in the study; therefore, consent to participate is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: cancer J Clin 2024/05/01. 2024;74(3):229–63. https://doi.org/10.3322/caac.21834.
2. Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut. 2023;72(2):338. https://doi.org/10.1136/gutjnl-2022-327736.
3. Jass JR. Do all colorectal carcinomas arise in preexisting adenomas? World J Surg 1989/01/01. 1989;13(1):45–51. https://doi.org/10.1007/BF01671153.
4. Winawer Sidney J, Zauber Ann G, Ho May N, et al. Prevention of Colorectal Cancer by Colonoscopic Polypectomy. N Engl J Med. 1993;329(27):1977–81. https://doi.org/10.1056/NEJM199312303292701.
5. Dik VK, Gralnek IM, Segol O, et al. Multicenter, randomized, tandem evaluation of EndoRings colonoscopy–results of the CLEVER study. Endoscopy Dec. 2015;47(12):1151–8. https://doi.org/10.1055/s-0034-1392421.
6. Rees CJ, Rajasekhar PT, Wilson A, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut. 2017;66(5):887. https://doi.org/10.1136/gutjnl-2015-310584.
7. Hassan C, Wallace MB, Sharma P, et al. New artificial intelligence system: first validation study versus experienced endoscopists for colorectal polyp detection. Gut. 2020;69(5):799. https://doi.org/10.1136/gutjnl-2019-319914.
8. Nutalapati V, Kanakadandi V, Desai M, Olyaee M, Rastogi A. Cap-assisted colonoscopy: a meta-analysis of high-quality randomized controlled trials. Endoscopy Int open. 2018;6(10):E1214–23. https://doi.org/10.1055/a-0650-4258.
9. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol Feb. 2006;101(2):343–50. https://doi.org/10.1111/j.1572-0241.2006.00390.x.
10. Tappenden P, Chilcott J, Eggington S, Patnick J, Sakai H, Karnon J. Option appraisal of population-based colorectal cancer screening programmes in England. Gut May. 2007;56(5):677–84. https://doi.org/10.1136/gut.2006.095109.
11. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of benefits, Burden, and Harms of Colorectal Cancer screening strategies: modeling study for the US Preventive Services Task Force. Jama Jun. 2016;21(23):2595–609. https://doi.org/10.1001/jama.2016.6828.
12. Siebert U. When should decision-Analytic modeling be used in the Economic Evaluation of Health Care? Eur J Health Econ. 2003;4(3):143–50.
13. Zhao S, Wang S, Pan P, et al. Magnitude, risk factors, and factors Associated with Adenoma Miss Rate of Tandem Colonoscopy: a systematic review and Meta-analysis. Gastroenterol May. 2019;156(6):1661–e167411. https://doi.org/10.1053/j.gastro.2019.01.260.
14. Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. Am J Gastroenterol Mar. 2004;99(3):519–22. https://doi.org/10.1111/j.1572-0241.2004.04070.x.
15. Moriichi K, Fujiya M, Sato R et al. Back-to-back comparison of auto-fluorescence imaging (AFI) versus high resolution white light colonoscopy for adenoma detection. BMC Gastroenterology. 2012;12(1):75. https://doi.org/10.1186/1471-230X-12-75
16. Pioche M, Denis A, Allescher HD, et al. Impact of 2 generational improvements in colonoscopes on adenoma miss rates: results of a prospective randomized multicenter tandem study. Gastrointest Endoscopy Jul. 2018;88(1):107–16. https://doi.org/10.1016/j.gie.2018.01.025.
17. Ikematsu H, Saito Y, Tanaka S, et al. The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy. J Gastroenterol Oct. 2012;47(10):1099–107. https://doi.org/10.1007/s00535-012-0575-2.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557
19. Shao L, Yan X, Liu C, Guo C, Cai B. Effects of Ai-assisted colonoscopy on adenoma miss rate/adenoma detection rate: a protocol for systematic review and meta-analysis. Medicine. 2022;101(46).
20. Brand EC, Dik VK, van Oijen MGH, Siersema PD. Missed adenomas with behind-folds visualizing colonoscopy technologies compared with standard colonoscopy: a pooled analysis of 3 randomized back-to-back tandem colonoscopy studies. Gastrointest Endosc. 2017;86(2):376–e3852. https://doi.org/10.1016/j.gie.2016.12.025.
21. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy Oct. 2013;45(10):842–51. https://doi.org/10.1055/s-0033-1344548.
22. Hassan C, Antonelli G, Dumonceau J-M 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
23. European Colorectal Cancer Screening Guidelines, Working G, von Karsa L, Patnick J, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 12/04. 2013;45(1):51–9. https://doi.org/10.1055/s-0032-1325997.
24. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-society Task Force on Colorectal Cancer and the American Cancer Society. *CA: a cancer journal for clinicians*. May-Jun. 2006;56(3):143–59. quiz 184-5.
25. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up after Colonoscopy and Polypectomy: a Consensus Update by the US Multi-society Task Force on Colorectal Cancer. Gastroenterology. 2020;158(4):1131–e11535. https://doi.org/10.1053/j.gastro.2019.10.026.
26. Min M, Deng P, Zhang W, Sun X, Liu Y, Nong B. Comparison of linked color imaging and white-light colonoscopy for detection of colorectal polyps: a multicenter, randomized, crossover trial. Gastrointest Endoscopy Oct. 2017;86(4):724–30. https://doi.org/10.1016/j.gie.2017.02.035.
27. Yang JF, Tang SJ, Lash RH, Wu R, Yang Q. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. Archives Pathol Lab Med Mar. 2015;139(3):388–93. https://doi.org/10.5858/arpa.2013-0523-OA.
28. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals Intern Med Oct. 2011;18(8):529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.
29. Leeflang MMG, Deeks JJ, Takwoingi Y, Macaskill P. Cochrane diagnostic test accuracy reviews. Syst Reviews. 2013;10:2:82–82. 07 05/24/received 09/18/accepted.
30. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol Jan. 2008;61(1):41–51. https://doi.org/10.1016/j.jclinepi.2007.03.016.
31. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med Dec. 2010;20(29):3046–67. https://doi.org/10.1002/sim.4040.
32. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Mental Health. 2019;22(4):153. https://doi.org/10.1136/ebmental-2019-300117.
33. Viechtbauer W. Conducting Meta-analyses in R with the metafor Package. J Stat Softw. 2010;08/05(3):1–48. https://doi.org/10.18637/jss.v036.i03.
34. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine*. Aug. 2009;18(4):W65–94.
35. Riu Pons F, Andreu M, Naranjo D et al. Narrow-band imaging and high-definition white-light endoscopy in patients with serrated lesions not fulfilling criteria for serrated polyposis syndrome: a randomized controlled trial with tandem colonoscopy. BMC Gastroenterology. 2020;20(1):111. https://doi.org/10.1186/s12876-020-01257-4
36. Gralnek IM, Siersema PD, Halpern Z, et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncol 02/20. 2014;15(3):353–60. https://doi.org/10.1016/S1470-2045(14)70020-8.
37. Hewett DG, Rex DK. Cap-fitted colonoscopy: a randomized, tandem colonoscopy study of adenoma miss rates. Gastrointest Endoscopy Oct. 2010;72(4):775–81. https://doi.org/10.1016/j.gie.2010.04.030.
38. Leufkens AM, DeMarco DC, Rastogi A, et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. Gastrointest Endoscopy Mar. 2011;73(3):480–9. https://doi.org/10.1016/j.gie.2010.09.004.
39. Halpern Z, Gross SA, Gralnek IM, et al. Comparison of adenoma detection and miss rates between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study. Endoscopy Mar. 2015;47(3):238–44. https://doi.org/10.1055/s-0034-1391437.
40. Papanikolaou IS, Apostolopoulos P, Tziatzios G, et al. Lower adenoma miss rate with FUSE vs. conventional colonoscopy with proximal retroflexion: a randomized back-to-back trial. Endoscopy May. 2017;49(5):468–75. https://doi.org/10.1055/s-0042-124415.
41. Triantafyllou K, Polymeros D, Apostolopoulos P, et al. Endocuff-assisted colonoscopy is associated with a lower adenoma miss rate: a multicenter randomized tandem study. Endoscopy Nov. 2017;49(11):1051–60. https://doi.org/10.1055/s-0043-114412.
42. De Palma GD, Giglio MC, Bruzzese D et al. Jan. Cap cuff-assisted colonoscopy versus standard colonoscopy for adenoma detection: a randomized back-to-back study. Gastrointestinal Endoscopy. 2018;87(1):232–240. https://doi.org/10.1016/j.gie.2016.12.027
43. Wang P, Liu P, Glissen Brown JR, et al. Lower Adenoma Miss rate of computer-aided detection-assisted colonoscopy vs routine White-Light Colonoscopy in a prospective Tandem Study. Gastroenterology. 2020;159(4):1252–e12615. https://doi.org/10.1053/j.gastro.2020.06.023.
44. Kamba S, Tamai N, Saitoh I, et al. Reducing adenoma miss rate of colonoscopy assisted by artificial intelligence: a multicenter randomized controlled trial. J Gastroenterol. 2021;08(8):746–57. https://doi.org/10.1007/s00535-021-01808-w. /01 2021.
45. Glissen Brown JR, Mansour NM, Wang P, et al. Deep Learning Computer-aided polyp detection reduces Adenoma Miss Rate: a United States Multi-center Randomized Tandem Colonoscopy Study (CADeT-CS trial). Clin Gastroenterol Hepatol. 2022;20(7):1499–e15074. https://doi.org/10.1016/j.cgh.2021.09.009.
46. Wallace MB, Sharma P, Bhandari P, et al. Impact of Artificial Intelligence on Miss Rate of Colorectal Neoplasia. Gastroenterology. 2022;163(1):295–e3045. https://doi.org/10.1053/j.gastro.2022.03.007.
47. Matsuda T, Saito Y, Fu KI, et al. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate?>--a pilot study. Am J Gastroenterol Aug. 2008;103(8):1926–32. https://doi.org/10.1111/j.1572-0241.2008.01931.x.
48. Bonnington SN, Rutter MD. Surveillance of colonic polyps: Are we getting it right? World J Gastroenterol. 02/14 07/27/received 10/15/revised 11/24/accepted. 2016;22(6):1925–1934. https://doi.org/10.3748/wjg.v22.i6.1925
49. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med. Apr 1993;1(13):901–6. https://doi.org/10.1056/nejm199304013281301.
50. Konishi F, Morson BC. Pathology of colorectal adenomas: a colonoscopic survey. J Clin Pathol Aug. 1982;35(8):830–41.
51. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy Sep. 1993;25(7):455–61. https://doi.org/10.1055/s-2007-1010367.
52. Castaneda D, Popov VB, Verheyen E, Wander P, Gross SA. Aug. New technologies improve adenoma detection rate, adenoma miss rate, and polyp detection rate: a systematic review and meta-analysis. Gastrointestinal Endoscopy. 2018;88(2):209–222.e11. https://doi.org/10.1016/j.gie.2018.03.022
53. Laiyemo AO, Doubeni C, Sanderson AK et al. Likelihood of missed and recurrent adenomas in the proximal versus the distal colon. Gastrointestinal Endoscopy. 2011;74(2):253–261. https://doi.org/10.1016/j.gie.2011.02.023
54. Lee J, Park SW, Kim YS, et al. Risk factors of missed colorectal lesions after colonoscopy. Medicine. 2017;96(27):e7468. https://doi.org/10.1097/md.0000000000007468.
55. Kim NH, Jung YS, Jeong WS et al. Miss rate of colorectal neoplastic polyps and risk factors for missed polyps in consecutive colonoscopies. Intestinal Res. 06/12 03/21/received 07/03/revised 07/04/accepted. 2017;15(3):411–8. https://doi.org/10.5217/ir.2017.15.3.411
56. Xiang L, Zhan Q, Zhao X-H et al. Risk factors associated with missed colorectal flat adenoma: a multicenter retrospective tandem colonoscopy study. World J Gastroenterology: WJG. 08/21 12/27/received 03/19/revised 05/29/accepted 2014;20(31):10927–37. https://doi.org/10.3748/wjg.v20.i31.10927.
57. Rembacken BJ, Fujii T, Cairns A, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet (London England) Apr. 2000;8(9211):1211–4.
58. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a north American population. Gastroenterol Jun. 2001;120(7):1657–65.
59. Terdiman JP, McQuaid KR. Surveillance guidelines should be updated to recognize the importance of Serrated polyps. Gastroenterology. 2010;139(5):1444–7. https://doi.org/10.1053/j.gastro.2010.09.024.
60. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterol Jun. 2010;138(6):2088–100. https://doi.org/10.1053/j.gastro.2009.12.066.
61. Anderson JC, Butterly LF, Colonoscopy. Quality indicators. Clin Translational Gastroenterol. 2015;02(26):e77. 10/29/received 01/26/accepted.
62. Ferlitsch M, Reinhart K, Pramhas S, et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing

screening colonoscopy. Jama Sep. 2011;28(12):1352–8. https://doi.org/10.1001/jama.2011.1362.
63. Jover R, Zapater P, Bujanda L, et al. Endoscopist characteristics that influence the quality of colonoscopy. Endoscopy Mar. 2016;48(3):241–7. https://doi.org/10.1055/s-0042-100185.
64. Rex DK, Bond JH, Winawer S, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-society Task Force on Colorectal Cancer. Am J Gastroenterol Jun. 2002;97(6):1296–308. https://doi.org/10.1111/j.1572-0241.2002.05812.x.
65. Kaminski MF, Wieszczy P, Rupinski M, et al. Increased rate of Adenoma Detection Associates with reduced risk of Colorectal Cancer and Death. Gastroenterol Jul. 2017;153(1):98–105. https://doi.org/10.1053/j.gastro.2017.04.006.
66. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med May. 2010;13(19):1795–803. https://doi.org/10.1056/NEJMoa0907667.
67. Yang PF, Wong SW. Adenoma Detection Rate in Colonoscopy: is indication a predictor? *Surgical laparoscopy, endoscopy & percutaneous techniques*. Apr. 2016;26(2):156–61. https://doi.org/10.1097/sle.0000000000000253.
68. Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterol Jun. 2007;132(7):2297–303. https://doi.org/10.1053/j.gastro.2007.03.032.
69. Hasegawa I, Yamamura T, Suzuki H, et al. Detection of colorectal neoplasms using linked Color Imaging: a prospective, randomized, Tandem Colonoscopy Trial. Clin Gastroenterol Hepatol. 2021;19(8):1708–e17164. https://doi.org/10.1016/j.cgh.2021.04.004.
70. Bisschops R, Tejpar S, Willekens H, De Hertogh G, Van Cutsem E. Virtual chromoendoscopy (I-SCAN) detects more polyps in patients with Lynch syndrome: a randomized controlled crossover trial. Endoscopy Apr. 2017;49(4):342–50. https://doi.org/10.1055/s-0042-121005.
71. Gupta N. How to improve your Adenoma Detection Rate during Colonoscopy. Gastroenterol Dec. 2016;151(6):1054–7. https://doi.org/10.1053/j.gastro.2016.10.008.
72. Subramanian V, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. Endoscopy Jun. 2011;43(6):499–505. https://doi.org/10.1055/s-0030-1256207.
73. Pilonis ND, Spychalski P, Kalager M, et al. Adenoma Detection Rates by Physicians and subsequent colorectal Cancer risk. Jama Feb. 2025;4(5):400–7. https://doi.org/10.1001/jama.2024.22975.
74. Suzumura EA, de Oliveira Ascef B, Maia FHA, Bortoluzzi AFR, Domingues SM, Farias NS, Gabriel FC, Jahn B, Siebert U, de Soarez PC. Methodological guidelines and publications of benefit-risk assessment for health technology assessment: a scoping review. BMJ Open. 2024;14(6):e086603. https://doi.org/10.1136/bmjopen-2024-086603
75. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM modeling Good Research practices Task Force-3. *Med Decis making*. Sep-Oct. 2012;32(5):690–700. https://doi.org/10.1177/0272989x12455463.
76. Fasterholdt I, Kjølhede T, Naghavi-Behzad M, et al. Model for ASsessing the value of Artificial Intelligence in medical imaging (MAS-AI). Int J Technol Assess Health Care Oct. 2022;3(1):e74. https://doi.org/10.1017/s0266462322000551.
77. Di Bidino R, Daugbjerg S, Papavero SC, Haraldsen IH, Cicchetti A, Sacchini D. Health technology assessment framework for artificial intelligence-based technologies. Int J Technol Assess Health Care Nov. 2024;21(1):e61. https://doi.org/10.1017/s0266462324000308.

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