

Adenoma Detection on Repeat Colonoscopy after Previous Inadequate Preparation

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recommendation for repeat exam >1 year (OR=11.0, 95% CI: 5.81 to 20.9).

CONCLUSION: The adenoma miss rate during colonoscopy with inadequate preparation is significantly higher than reported with tandem colonoscopy. Our findings support performing early repeat colonoscopy after inadequate preparation.

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Key words: Colonoscopy; Colorectal Neoplasms, Adenoma; Bowel preparation; Cathartics

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ABSTRACT

AIM: Inadequate bowel preparation is associated with reduced adenoma detection. We sought to determine whether the adenoma miss rate during colonoscopy with inadequate preparation is significantly greater than the adenoma miss rate reported with tandem colonoscopy.

METHODS: We reviewed records of all patients at our tertiary care center with an inadequately cleansed index colonoscopy between 2/1/2009-2/28/2010, who underwent repeat colonoscopy within 18 months. The primary endpoint was the overall adenoma miss rate. A two-sided test with alpha 0.05 had 80% power to distinguish an adenoma miss rate of about 33% compared to 22% reported with tandem colonoscopy. 910 patients had inadequate cleansing, and 127 met inclusion criteria including repeat colonoscopy within 18 months.

RESULTS: The overall adenoma miss rate was significantly greater than reported with tandem colonoscopy (52% vs. 22%, $p=0.001$). Miss rates were higher for all adenoma size categories (57% vs. 26% for <5 mm, $p=0.001$; 37% vs. 13% for 5-9 mm, $p=0.002$; 47% vs. 2% for ≥ 10 mm, $p=0.001$). Accounting for adenomas found on repeat, the recommended surveillance interval shortened for 27% of patients. Factors predicting failure to undergo repeat exam included cecal intubation (OR=3.99, 95% CI: 1.99 to 8.02) and endoscopist

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States. In 2010, 142,570 Americans were diagnosed with CRC and 51,370 died from the disease. Americans' lifetime risk for developing CRC is 1 in 19 for men and 1 in 20 for women^[1]. It is well established that adenomatous polyps are precursors to colon cancer^[2], and removal of adenomas during colonoscopy reduces the incidence of advanced adenomas and CRC, as well as CRC mortality^[3-9]. Given the reduction in mortality afforded by colonoscopy, multiple national guidelines recommend that Americans at average risk for CRC receive screening starting at the age of 50^[10-14]. Surveillance colonoscopy interval is guided by initial findings^[14].

Adequate bowel preparation is essential for quality colonoscopy. Inadequate preparation is associated with longer and more technically difficult procedures, greater likelihood of incomplete colonoscopy, shorter intervals between colonoscopies, and decreased polyp detection^[15-17]. Large studies have challenged the efficacy of colonoscopy for reducing the incidence and mortality of CRC in the proximal colon, and inadequate preparation is likely one important factor^[18,19]. Inadequate bowel preparation occurs in as many as 1/3 of colonoscopies^[15-17,20-24]. Predictors of inadequate preparation include

failure to comply with preparation instructions, later procedure start time, inpatient status, male sex, advanced age, obesity, diabetes, previous abdominal surgery, and medications that affect intestinal motility^[20-24]. Social and socioeconomic factors such as being unmarried, being non-Caucasian, requiring use of an interpreter, and having Medicaid insurance have been identified as high risk patient characteristics^[20,24,25]. Recently, it has become widely recognized that the timing of preparation administration is also critically important – dosing at least some of the purgative close to the time of colonoscopy increases the chance of adequate cleansing^[13,26,27].

In patients with inadequate preparation that cannot be overcome with operator techniques, a repeat colonoscopy is recommended to ensure detection of neoplasia^[14]. Two recent studies found a high number of adenomas on repeat colonoscopy after an index colonoscopy with inadequate preparation, but these investigations were done without comparison to established miss rates for colonoscopy. Establishing whether a repeat procedure after an inadequately cleansed colonoscopy yields statistically greater adenoma detection requires such a comparison^[28,29]. Tandem colonoscopy studies document the imperfect sensitivity of colonoscopy for adenoma detection^[30-33]. A 2006 meta-analysis of six such studies reported a colonoscopy miss rate for all adenomas of 22%, with miss rates of 2.1% for adenomas >9 mm, 13% for adenomas 5-9 mm, and 26% for adenomas 1-4 mm^[30]. The aim of this study was to determine whether the overall adenoma miss rate during colonoscopy with inadequate preparation is greater than the established adenoma miss rate observed with tandem colonoscopy.

METHODS

We conducted a retrospective review of all patients who underwent an initial colonoscopy (“index”) with an inadequate preparation between February 1, 2009, and February 28, 2010, and then underwent a repeat colonoscopy (“repeat”) within 18 months. Both procedures had to be performed at Thomas Jefferson University Hospital. This study was approved by Thomas Jefferson University’s Institutional Review Board.

The adequacy of the bowel preparation was determined at the time of colonoscopy by the physician performing the procedure using the Aronchick scale as defined in table 1^[34].

Table 1 Aronchick scale for bowel cleansing^[34].

RATING	DESCRIPTION
Excellent	Small volume of clear liquid or greater than 95% of surface seen
Good	Large volume of clear liquid covering 5% to 25% of the surface but greater than 90% of surface seen
Fair	Some semi-solid stool that could be suctioned or washed away but greater than 90% of surface seen
Poor	Semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen
Inadequate	Re-preparation needed

For this study, inadequate colon cleansing was defined as “fair,” “poor,” or “inadequate.” The default setting for evaluating the colon preparation in our electronic endoscopy database, EndoWorks® (Olympus America, Allentown, PA), during the study time period was “good,” and therefore the endoscopist was required to actively change the setting in the report to choose an alternative descriptor. Both outpatients and inpatients were included, and procedures were done by attendings as well as by GI fellows with attending supervision. Nearly all outpatient colonoscopies were done by an attending alone, while inpatient colonoscopies were typically performed by both a fellow and an attending. All colonoscopies were performed before the conceptualization of this study, and no endoscopist was aware

that the procedure findings would be analyzed.

Excluded were patients with a diagnosis of inflammatory bowel disease, hereditary colon cancer syndromes (hereditary nonpolyposis colorectal cancer syndrome, familial polyposis, etc.), previous colon resection, or age less than 50 years at time of index colonoscopy. Patients were also excluded when the index exam revealed adenocarcinoma, polyps that were intentionally not resected, or polyps removed in piecemeal fashion. Finally, we excluded colonoscopies performed by physicians primarily working at a satellite endoscopy site, as well as cases where the ambiguity of endoscopy and/or pathology results precluded accurate characterization of adenoma size, location, morphology, or histology.

EndoWorks® was queried for all patients with inadequate, fair, or poor preparation between the above dates. The records for each patient were reviewed to identify inclusion/exclusion criteria, as well as to determine if a repeat exam was performed within 18 months. Data abstracted from the colonoscopy reports included patient age, gender, indication for index colonoscopy, interval between colonoscopies, inpatient vs. outpatient status, preparation quality, extent of colonoscopy, and endoscopist recall recommendation. The pathology database was utilized for polyp assessments including the number of adenomas as well as the characteristics of each (size, location, presence of villous component, high grade dysplasia, and cancer). Instances where multiple specimens were placed in a single pathology container and the pathology report noted mixed histology – i.e. adenoma and non-neoplastic findings such as hyperplasia, lymphoid tissue or normal mucosa – were considered as a single adenoma regardless of the number of polyps placed in the jar. Based on the number and characteristics of the adenomas, the interval recall recommendation based on published guidelines was calculated for each patient at both timepoints^[14]. The guideline based recommendation after repeat exam considered all adenoma data from both colonoscopies.

The primary outcome of the study was the overall adenoma miss rate. Secondary outcomes included the miss rate for specific adenoma sizes (<5 mm, 5-9 mm, ≥10 mm) as well as the combined miss rate of advanced lesions (>1 cm, villous component, or high grade dysplasia) and malignancy. Analyses for change in surveillance recommendation from index to repeat and the rate of cecal intubation for both time points were also performed.

We estimated the adenoma miss rate as the number of new adenomas found at repeat colonoscopy divided by the total number of adenomas found at the index and repeat colonoscopy. Analyses of miss rates were based on logistic regression with the robust variance estimator to account for within-patient clustering (i.e., the correlation between multiple adenomas found in a patient). The main hypothesis was that the adenoma miss rate would be higher than the miss rate of 22% reported in a meta-analysis of tandem colonoscopies^[30]. Using a two-sided test with alpha 0.05, the study had 80% power to distinguish an adenoma miss rate of about 33% from the reported adenoma miss rate of 22%. We also estimated per-patient adenoma miss rates as the fraction of patients among whom new adenoma(s) were found during the repeat colonoscopy. Analyses of per-patient miss rates were also based on logistic regression.

RESULTS

Over 13 months, a total of 6,491 colonoscopies were performed at our institution. 910 patients had an inadequate preparation. 394 patients met exclusion criteria, leaving 516 patients eligible for evaluation. Of those, 127 underwent repeat colonoscopy within 18 months (Figure 1).

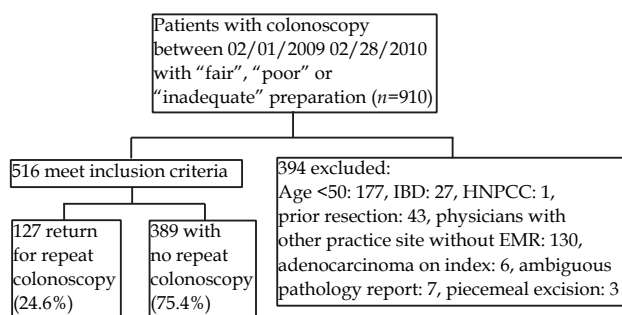


Figure 1. Flow chart of study design: IBD: Inflammatory Bowel Disease; HNPCC: Hereditary Non-Polyposis Colorectal Cancer; EMR: Electronic medical record.

These patients had a mean age of 61 years (range 50 to 88 years), were comprised equally of men and women, and were predominantly outpatients (>90%). Table 2 summarizes the study subject characteristics, and table 3 summarizes the colonoscopy characteristics and findings. Twenty-six physicians, all board certified in gastroenterology, performed the procedures included in this study. Fellows participated in 11 of 127 (9%) of index colonoscopies, and 39 of 127 (30%) of repeat colonoscopies.

As per protocol, all repeat colonoscopies were performed within 18 months of the initial colonoscopy (median = 5 months). For the repeat procedures, the preparation was adequate in 60%, and the cecum was intubated more often as compared to the index colonoscopy (92% vs. 67%). The polyp and adenoma miss rates are summarized in table 4.

For all size lesions, the estimated miss rate was 52% for both polyps (167/324) and adenomas (79/152). The adenoma miss rate was significantly higher than the miss rate reported in studies of tandem colonoscopy (52% vs. 22%, $p=0.001$)³⁰. Adenoma size did not significantly affect the miss rate (<5 mm=57%, 5-9 mm=37%, >10mm=47%; $p=0.174$). Furthermore, for each size category, these miss rates were significantly higher than the corresponding miss rates reported in tandem colonoscopies (57% vs. 26% for <5 mm, $p=0.001$; 37% vs. 13% for 5-9 mm, $p=0.002$; and 47% vs. 2% for ≥ 10 mm, $p=0.001$)³⁰. Adenoma miss rates did not vary by colon segment or when analyzed as “proximal” (proximal to splenic flexure) or “distal” (splenic flexure to rectum) (53% vs. 52%, $p=0.947$). Adenoma miss rates were also similar between screening colonoscopies and those procedures performed for surveillance or symptoms – 56% and 51%, respectively. Finally, the combined miss rate for advanced adenoma and cancer (including 1 carcinoid on repeat) was 42% (8/19).

The repeat colonoscopy found at least one polyp not identified by the initial colonoscopy in 71 patients, corresponding to a per-patient polyp miss rate of 56% (95% CI: 47% to 64%). A total of 49 patients had at least one additional adenoma detected, corresponding to a per-patient adenoma miss rate of 39% (95% CI: 31% to 47%). This was significantly higher than the per-patient adenoma miss rate reported in tandem colonoscopies of 30% ($p=0.036$)³³. The per-patient advanced adenoma miss rate was 6.2% (8/127).

The distribution of adenomas was similar for both the index and repeat colonoscopy. Only 10% (8/79) of the adenomas detected on the repeat colonoscopy were found in segments of the colon that were not intubated on the index colonoscopy – with two each in the cecum, right colon, hepatic flexure, and transverse colon. When analyzing only the cases which had cecal intubation on both the index and repeat procedures ($n=80$), the adenoma miss rate was 47% (56/118), with a per-patient miss rate of 44% (35/80). Only one of the eight advanced adenomas discovered on repeat colonoscopy was found in a segment not visualized on index colonoscopy. The miss

Table 2 Summary of subject characteristics (N=127).

Age (years), mean±sd	61	±9
Age (years), n (%)		
50-59	65	(51)
60-69	37	(29)
70+	25	(20)
Sex, n (%)		
Male	63	(50)
Female	64	(50)
Time between initial and repeat colonoscopy (months), mean±std		
6	±5	
Time between initial and repeat colonoscopy (months), n (%)		
0-3	40	(32)
4-6	36	(28)
7-12	26	(20)
>12	25	(20)

Table 3 Summary of colonoscopy characteristics and findings (N=127).

	INDEX	REPEAT
Indication for colonoscopy, n (%)		
Screening	43 (34)	
Surveillance	36 (28)	
Symptoms	48 (38)	
Disposition status of colonoscopy, n (%)		
Outpatient	115 (91)	115 (91)
Inpatient	12 (9)	12 (9)
Prep quality of colonoscopy, n (%)		
Inadequate (inadequate/poor/fair)	127 (100)	51 (40)
Adequate (good/excellent)	0	76 (60)
Extent of colonoscopy, n (%)		
Cecum/ileum	85 (67)	117 (92)
Right/ascending colon	12 (9)	2 (2)
Transverse colon	20 (16)	4 (3)
Left/descending colon	7 (6)	2 (2)
Sigmoid	2 (2)	1 (1)
Rectum/rectosigmoid	1 (1)	1 (1)
Polyps per patient, mean±sd		
1.2 ± 2.5		1.3 ± 1.7
Polyps per patient, n (%)		
0	67 (53)	56 (44)
1	31 (24)	28 (22)
2	8 (6)	20 (16)
3+	21 (17)	23 (18)
Adenomas per patient¹, mean ± sd		
0.6 ± 1.0		0.6 ± 1.1
Adenomas per patient¹, n (%)		
0	85 (67)	78 (61)
1	25 (20)	31 (24)
2	9 (7)	12 (9)
3+	8 (6)	6 (5)
Advanced adenomas or malignancy per patient¹, mean±sd		
0.09±0.31		0.07±0.26
Advanced adenomas or malignancy per patient¹, n (%)		
0	117 (92)	118 (93)
1	9 (7)	8 (7)
2	1 (1)	0 (0)

¹ One carcinoid found during the repeat colonoscopy.

Table 4 Summary of polyp and adenoma miss rates.

	INDEX	REPEAT	Miss rate (95% CI)
Polyps	157	167	52% (42%, 61%)
Adenomas	73	79	52% (43%, 61%)
By adenoma size:			
Small (<5 mm)	45	60	57% (46%, 67%)
Medium (5-9 mm)	19	11	36% (20%, 58%)
Large (≥ 10 mm)	9	8	47% (27%, 69%)
By adenoma location:			
Proximal colon (cecum, ascending, hepatic flexure, transverse)	47	52	52% (42%, 63%)
Distal colon (splenic flexure, descending, sigmoid, rectum)	25	27	52% (37%, 67%)
Advanced adenomas or malignancy¹	11	8	42% (22%, 65%)

¹ One carcinoid found during the repeat colonoscopy.

rate for advanced adenomas when both index and repeat colonoscopy achieved cecal intubation was 39% (7/18).

Guideline-based^[14] recall recommendations were analyzed for 126 cases and are summarized in Table 5.

One case was excluded because a carcinoid was found on repeat colonoscopy for which there is no standard recall recommendation. When the additional adenoma findings were considered, the recall recommendation following the repeat colonoscopy shortened for 34 (27%) patients (Table 6).

Table 5 Summary of guideline-derived^[14] recall recommendations (N=126).

	INDEX	REPEAT
Standard recall recommendation (years), n (%)		
1	0	1 (1)
3	16 (13)	30 (24)
5-10	26 (21)	38 (30)
10	84 (67)	57 (45)

Table 6 Change in guideline-derived^[14] recommendation for interval colonoscopy after repeat colonoscopy.

Change in follow up interval by guideline after results of repeat colonoscopy	Number of patients
3 years → 1 year	1
5-10 years → 3 years	6
10 years → 3 years	9
	18
10 years → 5-10 years	Total: 34 (27%)

Multivariable logistic regression was used to assess predictors of the likelihood of a patient returning for a repeat colonoscopy. The extent of intubation and the endoscopist's recall recommendation at the index procedure were both significant factors ($p=0.001$ for both). Cecal intubation was associated with a fourfold increase in the odds of no repeat colonoscopy (OR=3.99, 95% CI: 1.99 to 8.02). In addition, compared to cases with an endoscopist recall recommendation of 1 year or less, cases with an unavailable recall recommendation and those with a recall recommendation longer than 1 year both had increased odds of no repeat colonoscopy (OR=11.0, 95% CI: 5.81 to 20.9, and OR=31.3, 95% CI: 7.41 to 132, respectively). Controlling for these two variables, the likelihood of a repeat colonoscopy was marginally higher in men than in women ($p=0.096$), as well as with increasing number of polyps and the presence of any high-risk adenoma at the index colonoscopy ($p=0.085$ and 0.093 , respectively). However, presence of an adenoma was not a significant factor ($p>0.10$) in predicting likelihood of repeat colonoscopy. Finally, analyzing the 227 cases which had recall recommendations of 1 year or earlier, the recall recommendation was significantly associated with the likelihood of repeat ($p=0.001$), with longer recall recommendations having lower chances of repeat ("immediate": 46/63=73%; 0-3 months: 18/27=67%; 3-6 months: 23/44=52%; 6-12 months: 22/93=24%).

DISCUSSION

Inadequate colonoscopy preparation has a large impact on adenoma detection. With an "early repeat" window of 18 months, our study found an overall adenoma miss rate of 52% in patients who had an initial colonoscopy with inadequate preparation. Our study demonstrates that the miss rate with inadequate colon cleansing is significantly greater than that reported in tandem colonoscopy studies (52% vs. 22%). Significantly greater miss rates with inadequate colon cleansing were found for all adenoma size categories as well as for advanced lesions. The significantly greater miss rate after inadequate

cleansing was also observed when analyzed on a per-patient basis (39% vs. 30%). The discovery of additional adenomas at repeat colonoscopy shortened the recommended surveillance interval in 27% of patients.

Recent studies published by Lebwohl, *et al* and Chokshi, *et al* reported adenoma miss rates of 35% and 48%, respectively, when colonoscopy is repeated within 1 year of a colonoscopy with suboptimal preparation^[28,29]. Our study expands on these findings and differs in some important ways. First, we have demonstrated that the adenoma miss rate is significantly greater with inadequate cleansing than the reported miss rate with tandem colonoscopy^[30]. Another differentiating factor is that our study included all patients returning for repeat colonoscopy regardless of the preparation at the time of follow up. In this study, 40% of colonoscopies repeated for inadequate preparation were once again deemed inadequate with respect to colon cleansing. As having a history of inadequate cleansing increases the risk for future suboptimal cleansing^[35], inclusion of such patients permits a more realistic and generalizable estimate of the performance of a short interval repeat exam for the detection of adenomas.

The colonoscopies performed in our study were done for a variety of reasons including screening, surveillance, and symptoms. This mixed population may have had a greater risk for adenomas compared to a uniform group with an indication of screening. A meta-analysis of tandem colonoscopy studies served as the comparator group for our study^[30]. The meta-analysis was comprised of 6 individual studies - two in which the patient population was "high risk for polyps," one in which patients were "medium to high risk" for polyps, one in which patients were "medium to low risk," and finally two studies which could not be assessed for adenoma risk due to insufficient reporting of indications for colonoscopy. Only one of the six studies had a majority of screening colonoscopies, and two studies did not include any screening colonoscopies. Our study population seems comparable to the heterogenous population analyzed in this meta-analysis of tandem colonoscopy studies. However, our study does not establish whether significant miss rates would occur in a group of patients with a homogenous indication for colonoscopy.

While current guidelines do not specify a time period for follow-up after an inadequate preparation, it is recommended that "a repeat examination should be performed if the bowel preparation is not adequate before planning a long-term surveillance program^[14]." Endoscopists vary considerably in their recommendations following inadequate cleansing. These may range widely and include recommending prompt repeat examination^[36], repeat within one year^[28], a non-specific shortening of the guideline directed interval^[37], or no deviation at all. Notably, many risk factors for inadequate preparation, such as advanced age^[22], male sex^[20], and obesity^[23], are also risk factors for adenoma formation^[38-40]. The shared risks for adenoma formation and inadequate preparation lend further support to the recommendation for early repeat exam following inadequate colon cleansing.

As mentioned above, our study found that 40% of patients undergoing a repeat colonoscopy had a second inadequate preparation. Based on our findings, we recommend such patients return for a second early repeat exam. This emphasizes the need for an effective bowel preparation strategy following inadequate cleansing. Next-day colonoscopy after an inadequate preparation has been shown to reduce the risk of a second inadequate preparation^[35]. Endoscopists should consider this strategy, when feasible, for patients found to have an inadequate preparation.

We found that less than a quarter of patients returned for a repeat colonoscopy within 18 months of an exam with inadequate cleansing. The demographics did not differ between patients who returned early and those who did not. A retrospective study may miss many factors limiting detection of such follow up, both patient driven (change or loss of insurance, follow up outside our institution, change of residence, patient decision to not follow up, death, etc.), and physician driven (uncertainty of the importance of repeating the exam, reduced reimbursement, impact on physician colonoscopy quality measures, concern for patient inconvenience, etc.).

We identified two factors on the initial inadequately cleansed colonoscopy which were independently associated with the patient's failure to attend an early repeat colonoscopy – successful cecal intubation and recall recommendations that were either >1 year or absent. In the subgroup of patients receiving a recommendation to repeat the exam within 1 year, compliance with recall fell precipitously when the recommendation exceeded 6 months.

Our study has several limitations. The retrospective design may have contributed to incomplete or inaccurate data collection, and necessitated reliance on a qualitative scale^[33] for colon cleansing already in place. At the time the colonoscopies were performed, the default preparation rating was “good” and required a conscious decision by the physician to change the grade. It is probable that additional colonoscopies that would have met our definition of inadequate were not included in this study as a result of physicians’ failure to change this default setting. Furthermore, endoscopists were aware of the findings on index colonoscopy, and this may have affected their approach and thoroughness during the second procedure. While we did not have access to withdrawal times to compare the duration of inspection during each colonoscopy, we would not expect the level of thoroughness to exceed that of a prospective tandem colonoscopy study, which is expressly performed to assess adenoma miss rate. Importantly, the endoscopists were not aware that their colonoscopies would be analyzed, thus preventing any deviation from their normal pattern of mucosal inspection, as well as their normal practice of recommendations for follow up colonoscopy. Additionally, adenoma morphology was not assessed due to the retrospective design. The effect of inadequate preparation on the detection of flat lesions, which have greater risk for advanced histologic findings, may be important and would best be addressed using a prospective design^[41]. Finally, our study was performed at a single center and the findings may not be generalizable to all settings.

While consistent and conservative rules for establishing the number, size, and characteristics of polyps and adenomas were used, retrospective review of this data may have led to classification errors. In fact, our overall adenoma detection rate, combining the index and repeat colonoscopies, was high although still within reported detection rates^[42]. This may be at least partly explained by several factors including the fact that each patient underwent two colonoscopies, a high percentage of colonoscopies were performed for adenoma surveillance or symptoms, and a moderate number of patients were of advanced age.

The physician’s assessment of colon cleansing was based on a validated qualitative scale^[34] and did not utilize one of the more recently validated quantitative scales^[43,44]. Therefore, there may have been greater intra- and inter-physician variation in judging the adequacy of colon cleansing than afforded by a quantitative scale. The numbers of colonoscopies per physician were too small to reliably evaluate this. Regardless, the finding of inadequate cleansing using this grading scale commonly used in clinical practice was

associated with a significantly elevated adenoma miss rate.

In conclusion, the miss rate for adenomas is significantly greater during colonoscopy with inadequate preparation. This is consistent for all adenomas and across all adenoma size categories evaluated. Most patients who underwent an inadequately cleansed colonoscopy did not return for a repeat exam within 18 months. Two independent factors on the initial colonoscopy predicted failure to return – achieving cecal intubation, and physician failure to recommend an early repeat exam within 1 year. These findings support the recommendation for an early repeat colonoscopy following an inadequately cleansed exam. A prospective study would be valuable to eliminate the inherent shortcomings of a retrospective study and to confirm these findings.

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Colin L Smith and Abhik Roy contributed equally to this work.

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