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A pilot study for using high-volume colon irrigation bowel preparation for colon capsule endoscopy shows feasibility of adequate bowel prep with high patient satisfaction

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ABSTRACT

A feasibility study was performed to test a bowel preparation (BP) method that would improve patients' experience of colon capsule endoscopy (CCE) while retaining clinical adequacy. Specifically, the use of high-volume colon irrigation with the Hygieacare[®] System, HygiPrep[™], was tested in conjunction with Medtronic's PillCam COLON 2 Capsule. This prospective, single-center, and IRB-approved study evaluated HygiPrep use prior to the PillCam COLON 2 procedure instead of the standard split-polyethylene glycol-electrolyte (PEG) oral prep. The study was performed at Austin Gastroenterology (Austin, TX), and all capsule video files were forwarded to a Central Reader to evaluate and compile a study report. Six of the seven (86%) subjects completed both the HygiPrep and PillCam COLON 2 exams and were graded as excellent, good, or adequate by the Central Reader. Patients' feedback reported positive satisfaction scores for both the HygiPrep and the PillCam COLON 2 procedures. These results support our hypothesis that HygiPrep was as effective as Split-PEG BP. We suggest that the HygiPrep, is a suitable BP for CCE, providing adequate BP and high patient satisfaction.

Keywords: Capsule Endoscopy; Colon Capsule Endoscopy; Colon Preparation; Colonoscopy Quality; HygiPrep; PillCam; COLON 2

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Introduction

Colon capsule endoscopy (CCE) has proven to be an important non-invasive tool for colorectal cancer (CRC) screening and for diagnosing and monitoring changes in the gastrointestinal mucosa. The clinical success of CCE, defined as accurate detection of polyps or inflammation, can only be achieved in a completely clean colon [1]. CCE is especially sensitive to colon cleanliness since the procedure, unlike colonoscopies, does not include air insufflation and suction, often used to improve cleanliness. Therefore, the quality of the bowel preparation (BP) is a significant factor when determining the clinical outcome of capsule endoscopy [2]. The Hygieacare® System is intended for colon cleansing when medically indicated, such as before a radiological or endoscopic examination. The HygiPrep™ is a BP for colonoscopy performed using the Hygieacare System. It has been well studied and proven to be safe, effective, and well-tolerated by patients [3–7], with over 8,000 procedures performed at the study location (AG-Hygieacare, Austin, TX, August 2015-September 2020). The HygiPrep has proven to provide 97% adequacy, even in patients with poor BP predictors such as age, male sex, and co-morbidities. Furthermore, the well-established and validated protocols have high patient satisfaction rates and much fewer side effects than the standard split-PEG prep [3]. The PillCam® Endoscopy System, PillCam COLON 2 Capsule, provides a minimally invasive procedure for effective colonic luminal visualization [8–11]. It provides excellent visualization of the large intestine mucosa and allows colon exploration without sedation and gas insufflation [12]. The PillCam COLON 2 Endoscopy Capsule has good tolerability in well-selected patients [13] and is FDA approved in patients for whom a complete evaluation of the colon was not technically possible and patients with major risks for colonoscopy or moderate sedation. The European Society for Gastrointestinal Endoscopy suggests that CCE is a reasonable alternative to colonoscopy for CRC in average-risk patients [14]. The US

Multisociety Task Force on CRC recommended CCE as a tier 3 recommendation [15]. Inadequate BP can lead to lower detection rates of adenomas and sessile serrated polyps (SSP) and increased morbidity and mortality risk. It can also lead to additional procedure time, canceled visits, wasted resources, and potential lack of reimbursement [10,16]. Since it is impossible to wash or aspirate during a CCE, superior BP is required. Currently, CCE prep involves ingestion of a 4L polyethylene glycol-electrolyte (PEG) solution followed by one or two "SUPREP boosters" as directed by the device recorder [10,16]. It is well recognized that even standard high-volume oral purgatives have notable patient dissatisfaction and often intolerance, resulting in inadequate colon preparation [17]. Therefore, the standard high-volume oral purgative-based protocol for PillCam COLON 2 Capsule imposes a high burden on patients and may limit their CCE acceptance [18].

Here, we present a feasibility study to explore the Hygieacare high-volume colon irrigation use to replace the oral-purgative prep in the PillCam COLON 2 protocol. The hypothesis was that the HygiPrep will be easier for the patients to tolerate than the standard BP, and that BP adequacy will be equivalent to the existing oral preparation.

Methods

The high-volume colon irrigation bowel prep - HygiPrep™

The Hygieacare System illustrated in Figure 1 (left panel) is intended for colon cleansing when medically indicated, such as before a radiological or endoscopic examination. HygiPrep is performed on the same day of the colonoscopy, prior to the examination procedure. Temperature controlled, double filtered, tap water is introduced by gravity at a comfortable temperature into the large intestine, thus cleansing the colon of its contents. It is hygienic, and almost all patients find it to be comfortable and painless. The water flow, adjustable by the patient's needs, flows through a disposable tubing and a sterile, disposable rectal nozzle. The patient is seated on the

disinfected basin and the sterile nozzle is introduced into their rectum (1-2 inches). A gentle stream of water then flows into the bowel, loosening stool, allowing the patient to comfortably and discreetly evacuate their colon. Water continues to flow and gently cleans the colon until the practitioner instructs the patient on completion of the procedure. The average procedure time of the HygiPrep is an hour. All

bowel preparations with the system are performed based on a physician's prescription and by certified practitioners trained on the safe use of the system and under stringent and validated standard operating procedures (SOP). When used as preparation for colonoscopies, the bowel cleansing is referred to as HygiPrep and performed under specific and designated SOPs for BP.

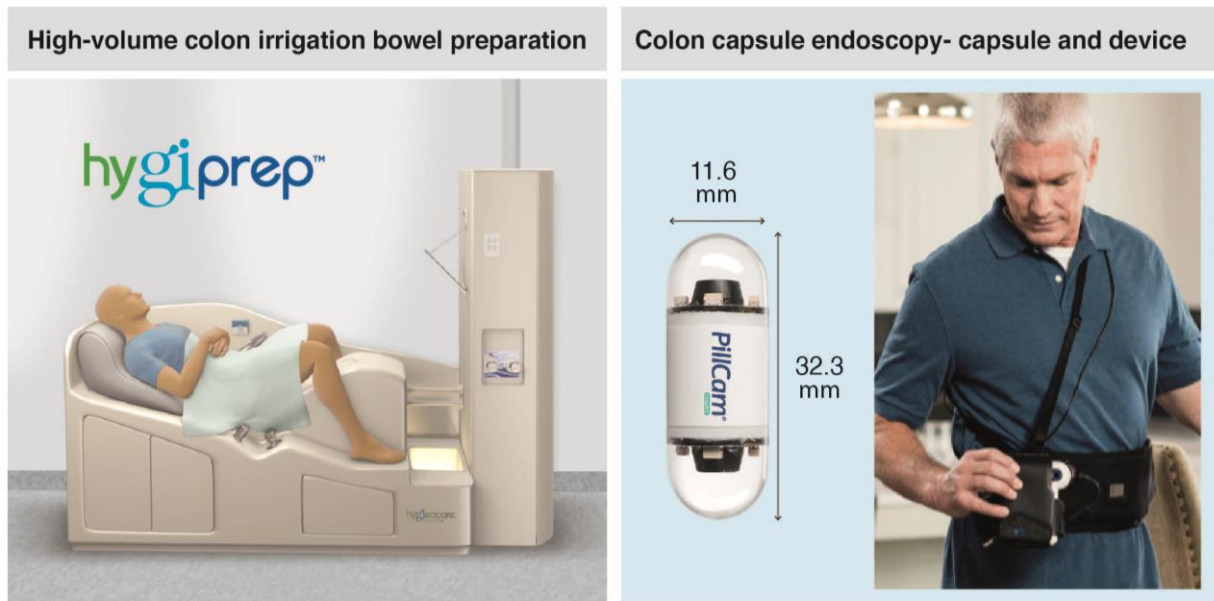


Figure 1 Left - Illustration of the FDA-cleared, prescription-only, Hygieacare[®] system for high-volume colon irrigation system, operating under stringent standard operating procedures (SOP). They HygiPrep[™] is a high-volume colon irrigation bowel prep, replacing the traditional oral prep; Right - the Medtronic[®] PillCam[™] COLON 2 capsule with dimensions and a picture presenting the device as worn by a patient.

CCE- The PillCam[™] COLON 2 Endoscopy System

The Medtronic[®] second generation CCE, PillCam COLON 2 endoscopy Capsule, is 32.3 mm in length and has a diameter of 11.6 mm and two wide angle cameras, with a field of view of 172 degrees each, enabling nearly 360 degree viewing of the mucosa (Figure 1, right panel). It may be used for detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and when a complete evaluation of the colon was not technically possible. In addition, it is intended for detection of colon polyps in patients with evidence of gastrointestinal bleeding of lower GI origin. This applies only to patients with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy and moderate

sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy. The system utilizes an adaptive image acquisition rate depending on capsule propulsion speed with 35 frames per second during active movement, and 4 frames per second during the stationary period. It uses high resolution imaging below 0.1 mm, with a magnification of 1 to 8. The data recorder (DR3) includes an alarm system that recognizes the capsule's position and sends the patient signals when booster medications are required^[1]. On the day of the procedure, the patient receives audible alerts from the external data recorder that displays the instructions (Figure 1, right panel). Patients resume most of their daily activities without laying down or sleeping until they receive an "End of Procedure" notification.

Clinical study design

This prospective, single-center, study objectives were to evaluate the effectiveness of the HygiPrep when used in combination with the PillCam COLON 2 and to assess the patients' satisfaction with the HygiPrep BP as part of a CCE procedure. The institutional review board (IRB)-approved clinical investigation allowed ten healthy participants to undergo a PillCam COLON 2 procedure using HygiPrep as the BP method to replace the 4 L Split-PEG oral prep (ClinicalTrials.gov Identifier: NCT03458390). The standard prep protocol following the guidelines of the US Registration Study for PillCam COLON 2 includes Sennosides tablets (4X12 mg) two days before the procedure, 24 hours of clear liquid diet (CLD) before the procedure, 2 L PEG on the night before the procedure, additional 2 Liter PEG on the day of the procedure and then *nil per os* (NPO, nothing by mouth) until ingestion of the PillCam COLON 2. The modified protocol approved for our study design included a normal diet and 10 glasses of water two days before the procedure, CLD 24 hours before ingestion, Bisacodyl (2X5 mg) at 2 pm and 8 pm, and NPO from midnight on the day before the procedure. On the day of the procedure, patients were instructed to take Bisacodyl (2X5 mg) at 6 am and then underwent the HygiPrep at 8 am, before capsule ingestion at 9 am. Detailed dietary and medical instructions and the timeline for capsule ingestion are presented in Figure 2. The study outcomes assessment was defined as BP adequacy for the primary endpoint and patient satisfaction and adverse event (AE) as secondary endpoints. Exclusion criteria were the same as for both the FDA-cleared products. AEs noted with the HygiPrep procedure include nausea, vomiting, dizziness, and abdominal cramping. Risks associated with capsule endoscopy include capsule retention, aspiration, and skin irritation.

Clinical study endpoints analysis

Of the ten patients enrolled, seven were able to meet the primary endpoint of the PillCam COLON passing through their colon within the

timeframe allotted by the PillCam's battery life. For three patients, HGP-0005-003, -006, and -008) the capsule did not progress to the descending colon prior to its battery life ending. These three patients were excluded from the study, and the following analysis does not include them. All seven patients that were able to meet the primary endpoint, were also able to complete the HygiPrep, and were included in the analysis.

Central reader analysis

Each capsule endoscopy video was evaluated by a single highly experienced central reader who documented the findings in the CCE Report. Colon cleanliness during capsule endoscopy was graded and documented. The Report is intended to provide information on the quality of the preparation, technical details of the examination, completeness of the procedure, and note any significant findings. The established reporting criteria for adequacy is based on a four-point scale rated "excellent", "good", "fair", and "poor" (Table 1). It is expected that a BP rated as adequate will be able to detect polyps > 5 mm. For this study, only excellent and good were considered adequate. When detecting polyps or masses \geq 6 mm or 3 or more polyps, patients should be sent for post-CCE colonoscopy for polypectomy^[14].

Patients satisfaction evaluation

To estimate patients' satisfaction, all patients were provided with post-procedure satisfaction surveys. Patients evaluated their satisfaction with both the HygiPrep and the CCE procedure. For both surveys, responses were ranked: "Really good", "Good", "Bad", or "Really bad". The patients' responses to the survey were analyzed by counting responses in each category. Results are reported by rating and satisfaction percentages.

Results

The study analysis included seven patients that underwent HygiPrep™ followed by the PillCam™ COLON 2 CCE and met the primary endpoint of completing the capsule endoscopy examination. Of these seven patients, four males and three females, with an average age of

35±8 years (min=22, max=55). Four patients were Caucasian, one African-American, one Latino, and one Asian. The patients' average BMI was 28.6±5.6 (min=19.8, max=37.3). Three of the patients had no reported underlying diseases and the other patients had

hypertension and arthritis (HGP-0005-001), anemia (HGP-0005-005), anxiety disorder, hypercholesterolemia, hypothyroidism (HGP-0005-009), and asthma (HGP-005-0010). None of the patients reported opioid use or a history of chronic constipation.

A. PillCam™ COLON 2 protocol - using standard oral prep

Two days before procedure		One day before procedure	
<ul style="list-style-type: none"> • Sennosides tablets - 4 X 12 mg 		<ul style="list-style-type: none"> • 2 Liter PEG (the night before) 	<ul style="list-style-type: none"> • CLD (24 h)
Day of procedure			
<ul style="list-style-type: none"> • 2 Liter PEG & NPO • 9 am - ingestion of PillCam COLON 2 • Possible PillCam COLON 2 alerts – 0, 1, 2, 3, 4 to track capsule progression and guide patient if there is a need for additional medication. • Final PillCam COLON 2 alert – Once the capsule passed the colon, the patient can remove the device 		<ul style="list-style-type: none"> • 1 h post-ingestion – CLD until End of Procedure notification • At small bowel detection - Drink an additional 34 oz of water • 3 h post ingestion - Drink an additional 34 oz of water • 5 h post ingestion – Continue CLD and stay active • 7 h post ingestion – standard light meal, plenty of fluid, stay active 	

B. PillCam™ COLON 2 protocol- using HygiPrep™

Two days before procedure		One day before procedure	
<ul style="list-style-type: none"> • Normal diet & 10 glasses of water 		<ul style="list-style-type: none"> • 2 pm – 2 X 5 mg Bisacodyl • 8 pm – 2 X 5 mg Bisacodyl 	<ul style="list-style-type: none"> • CLD (24 h) • NPO after midnight
Day of procedure			
<ul style="list-style-type: none"> • 6 am – 2 X 5 mg Bisacodyl • 8 am – HygiPrep • 9 am - ingestion of PillCam COLON 2 • Possible PillCam COLON 2 alerts – 0, 1, 2, 3, 4 to track capsule progression and guide patient if there is a need for additional medication. • Final PillCam COLON 2 alert – Once the capsule passed the colon, the patient can remove the device 		<ul style="list-style-type: none"> • 1h post-ingestion – CLD until End of Procedure notification • At small bowel detection - Drink an additional 34 oz of water • 3 h post ingestion - Drink an additional 34 oz of water • 5 h post ingestion – Continue CLD and stay active • 7 h post ingestion – standard light meal, plenty of fluid, stay active 	

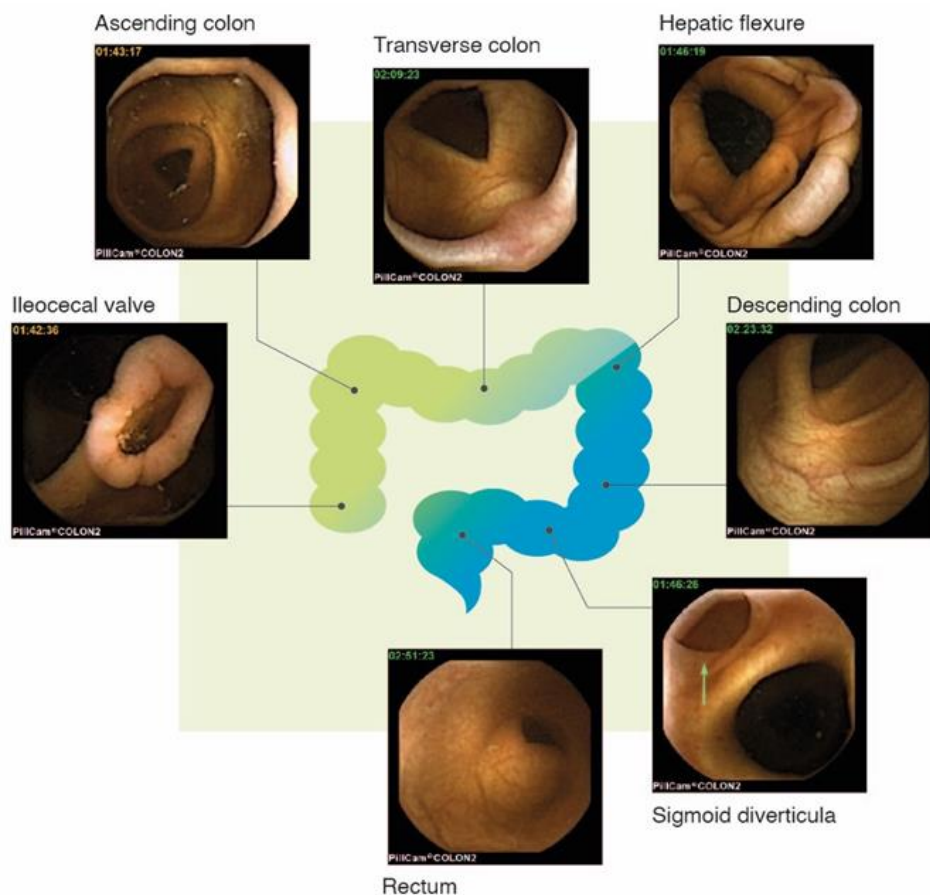
Figure 2 Description of the protocol for the PillCam™ COLON 2 prep procedure: A. The standard protocol, following the guidelines of the US Registration Study For PillCam COLON 2, and includes 4 L of Split-polyethylene glycol-electrolyte (PEG) oral prep; B. The modified protocol with the HygiPrep™ as the method for bowel preparation (BP). In blue - dietary instruction, in green - medication instructions. Abbreviation - CLD - clear liquid diet, NPO- *nil per os* (nothing by mouth).

Table 1 – Description of the cleanliness scale utilized by the central reader

Cleanliness Score	Description	Findings
4	Excellent	No more than minimal amounts of adherent feces
3	Good	Small amount of feces or dark fluid, but not enough to interfere with examination
2	Fair	Enough feces or dark fluid present to preclude a completely reliable examination
1	Poor	Large amount of fecal residue

Table 2 – Outcome scores by the central reader per patient, based on a four-point scale rated “excellent”, “good”, “fair”, and “poor”.

Patient ID	Ascending Colon Score	Transverse Colon Score	Descending Colon Score	Overall Score
HGP-0005-001	Excellent	Excellent	Excellent	Excellent
HGP-0005-002	Good	Good	Good	Good
HGP-0005-004	Excellent	Excellent	Excellent	Excellent
HGP-0005-005	Good	Good	Good	Good
HGP-0005-007	Fair	Fair	Good	Fair
HGP-0005-009	Excellent	Excellent	Excellent	Excellent
HGP-0005-010	Excellent	Excellent	Excellent	Excellent

**Figure 3** Images taken during the PillCam™ COLON 2 procedure and after the HygiPrep™ bowel prep, showing the capsule progression along the colon. Pictures were captured from the CCE videos of HGP-0005-005, rated as “Good”, and HGP-0005-010, rates as “Excellent”.

The HygiPrep allowed for recording of high-quality images, as demonstrated in Figure 3. Colon cleanliness was measured by the Central Reader on a 4-point scale as follows: “Excellent” = four patients (57%), “Good” = two patients (29%), and “Fair” = one patient (14%) (Tables 1 and 2). Six of the seven capsule video exams (86%) were deemed adequate, graded as “Excellent” or “Good” by the Central Reader; No patient was graded “Poor” (Figure 4). Only one of the capsule endoscopy videos had a

pathological finding (patient 005) and the endoscopist was notified of scattered diverticular disease, 1 cm sigmoid sessile polyp, mucosal erosions, mild erythema, and internal hemorrhoids. These findings were corroborated in a follow up colonoscopy. Adverse events were reported before and after the HygiPrep, on a 4-point scale: 1 = very little, 2 = some, 3 = quite a bit, and 4 = a lot. Of the seven patients, only one reported some nausea (level 2) both before and after the HygiPrep.

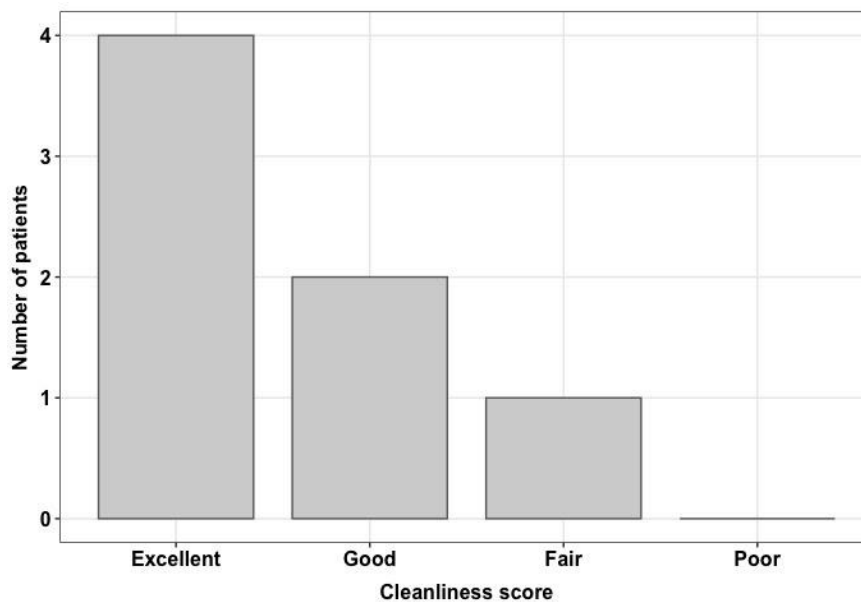


Figure 4 Cleanliness scores for the seven patients who met the study primary endpoint of passing the PillCam™ COLON 2 capsule and performed HygiPrep™ as the chosen bowel preparation (BP).

Patient Satisfaction was scored on a 4-point scale: 4= “Really good”, 3= “Good”, 2= “Bad”, 1= “Really bad”. Satisfaction was evaluated separately for the HygiPrep and the PillCam COLON 2 procedure. Of the seven patients who completed the protocol, six filled out the feedback reports. For the HygiPrep, five patients reported “Really Good” and one patient reported “Good”. All six patients reported “Really good” for the PillCam COLON 2 procedure.

Discussion

CCE is approved by the FDA for colon visualization and colon polyp detection in patients that cannot undergo complete colonoscopies and has been proposed as an alternative to colonoscopies in CRC screening [14]. CCE does not require sedation and allows the patient to keep active, thus having an

advantage over traditional optical colonoscopy. Unfortunately, the BP, critical for the success of the CCE imaging, is burdensome and involves oral intake of 4 L split-PEG, a task that is not also achievable by many patients. Since no additional cleansing can be performed mid-procedure when performing CCE, it is critical to achieve an adequate BP in the highest percentage of patients possible. The HygiPrep™ has been proven safe and effective in over 12,000 and is well tolerated by patients [3]. Over 8,000 HygiPrep were performed in the AG - Hygieacare center (Austin, TX), where this feasibility study took place (performed from August 2015- December 2019). Based on the Boston Bowel Preparation Score (BBPS), 97% of the HygiPrep performed in this center were adequate for colonoscopy. The HygiPrep has

also proven to be agnostic to many predictors for poor BP, including old age and several underlying diseases; this population is also, in part, the target population for CCE. In this study, we demonstrate that the HygiPrep BP provides a non-inferior BP in patients undergoing a CCE PillCam™ COLON 2 procedure and allowed recording of high-quality images that could be interpreted by a central reader (Figure 3).

Considered safe with very low rate of technical failures (3%) and a high capsule excretion rate of about 90% [12], CCE is an acceptable alternative for invasive colonoscopies. The excellent camera and recording abilities demonstrate CCE to be an effective tool in the diagnosis and surveillance of mucosal inflammation diseases. It may also provide an option for those patients who refuse colonoscopy or had an incomplete exam [19]. However, patients' acceptance is critical for the wide adoption of this technology and the associated BP protocol. The HygiPrep is associated with very high patient satisfaction and patients prefer it over traditional oral preparation [3]. In this study, patient satisfaction with both procedures was high, at the same time of keeping the required clinical adequacy.

Since CCE does not require patient sedation and is associated with significantly less discomfort than colonoscopies [20], this technology may be more readily accepted by patients and lead to better compliance with CRC recommendations. A Markov cost-effectiveness model found that high-volume colon irrigation, such as the HygiPrep, is much more cost-effective than traditional oral BP when considering both direct and indirect costs over a long-term period [6]. Using the HygiPrep as a BP of choice for PillCam COLON 2 procedures will allow patients to complete the prep and ingestion of the PillCam on the same day. It can also improve patients' satisfaction without reducing the quality of the clinical examination. We suggest that the combination of HygiPrep and the PillCam COLON 2 will increase patient preparation compliance and reduce costs associated with non-compliance and missed screening and

diagnostic colonoscopies. A larger non-inferiority study should follow this study to evaluate the combination of the PillCam COLON 2 and HygiPrep as an expanded indication.

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