

# Hydrogen Breath Testing Predicts Bowel Preparation Quality Prior to Colonoscopy: A Systematic Review

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## Abstract

**Background:** This systematic review aims to assess the accuracy of hydrogen breath testing as a predictor of bowel preparation.

**Methods:** Studies were identified from MEDLINE, Embase, Web of Science, Cochrane Library and clinicaltrials.gov. Two investigators evaluated abstracts for inclusion criteria - report of correlation between hydrogen breath levels and bowel preparation quality, prospective design and non-emergent colonoscopy in adults. Included studies underwent duplicate data extraction using a standardized approach. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool assessed quality of the studies.

**Results:** One hundred fifty-nine publications were identified, and six unique studies met inclusion criteria. The number of patients analyzed ranged from 61 to 127. Three studies were performed in the USA, one in Japan and two in Italy. Three studies used a prebiotic in addition to a purgative, with the intention of enhancing the discriminating ability of hydrogen breath levels. Three studies assessed baseline hydrogen levels. In five of the six studies, hydrogen breath levels were predictive of inadequate bowel preparation. Suggested absolute hydrogen levels to distinguish adequate from inadequate bowel preparation ranged from 3 to 10 parts per million. Depending on the cutoff value, sensitivity ranged from 71% to 100% and specificity from 87% to 100%. There was significant heterogeneity among studies in breath testing protocol and breath analyzer used. Full-text studies had low risk of bias in most assessed domains.

**Conclusion:** Hydrogen breath levels predict bowel preparation adequacy but existing studies have significant limitations. Further studies

should use standardized methods and consider the real-world practicality of self-administered home breath testing.

**Keywords:** Colonoscopy; Bowel preparation; Quality; Hydrogen; Breath test

## Introduction

Inadequate bowel preparation is a prevalent and persistent problem in the endoscopy unit. Even with state-of-the-art split-dose bowel preparations, 15-20% of patients have inadequate preparation at the time of colonoscopy [1]. Inadequate preparation results in multiple clinical and economic harms, including decreased adenoma and cancer detection, repeat procedures, patient burden and increased cost [2-4]. Thus, a fail-safe strategy based solely on the *prevention* of inadequate preparation remains elusive. An appealing parallel strategy is *detection* of patients with inadequate bowel preparation before they incur the risk and expense of sedation and colon intubation. Such an approach could be used to rapidly triage patients with inadequate preparation to interventions, such as same-day consumption of additional preparation.

One novel technique to detect bowel preparation quality is hydrogen breath testing (HBT). This test holds theoretical appeal - fermentable substrates passing from the small bowel into a bacteria-rich colon produce hydrogen gas, which is then absorbed into the blood stream and exhaled. Exhaled hydrogen would be expected to decrease after a successful bowel preparation, potentially offering a quantifiable measure of the adequacy of bowel preparation without instrumentation. Indeed, several small studies have suggested that HBT accurately predicts preparation quality prior to colonoscopy [5-9]. Given the appropriate technology, HBT could even be used either to help patients tailor the amount of purgative they consume at home, or to identify patients with inadequate preparation once they reach the endoscopy unit.

We sought to systematically review the literature for studies examining the diagnostic test characteristics of HBT for inadequate bowel preparation. Through this work, we hoped to assess the quality of the existing literature on this topic and derive summary estimates of the diagnostic test characteristics of HBT for inadequate bowel preparation.

Manuscript submitted August 24, 2018, accepted September 7, 2018

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doi: <https://doi.org/10.14740/gr1078w>

## Materials and Methods

### Study selection

We developed a systematic search strategy with the assistance of a medical librarian (MC). We submitted our protocol to PROSPERO, an international prospective database of systematic reviews, which approved it before we commenced our search (PROSPERO 2015: CRD42015017806). We searched MEDLINE, Embase, Web of Science, the Cochrane Library, and clinicaltrials.gov from database inception to May 2016. Embase was also used to identify abstracts from meetings of the American Gastroenterology Association, the American Society of Gastrointestinal Endoscopy and the American College of Gastroenterology. Clinicaltrials.gov was searched to identify recently completed or ongoing trials. Studies were not restricted by language. The search strategy included the terms “colonoscopy”, “breath test” and “hydrogen breath test”, or synonyms of those terms. The full search strategy is provided in the Supplementary 1.

Studies were included if they met the following criteria: 1) testing of hydrogen breath levels with the intention of predicting bowel preparation quality; and 2) performance of colonoscopy to formally assess bowel preparation quality (the gold standard). Studies were not restricted by the bowel preparation scale, the breath testing substrate or protocol that was used.

Two physicians from our team (AS and JK) independently screened all abstracts to determine whether they met inclusion criteria. When an abstract appeared to meet inclusion criteria, the full-text article, if one existed, was reviewed. Any disagreement on inclusion was adjudicated by a third-team member (SS). For studies that appeared relevant but published only in abstract form, we contacted the authors for additional information.

### Data extraction

A structured form was created to extract variables of interest, including study location and design, patient selection strategy, colonoscopy indication, age, gender, dietary changes, bowel purgative, timing of breath testing, substrate (e.g. lactulose, inulin, fiber), breath test analysis equipment, preparation quality scale, suggested hydrogen-level cutoffs and diagnostic test characteristics.

### Quality assessment

Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [10], which is recommended by the Cochrane handbook for the assessment of the accuracy of diagnostic tests [11]. This tool focuses on four domains: patient selection, index test, reference standard, and patient flow and index test timing. Two investigators (AS and JK) independently performed the quality assessment and agreed upon low, medium or high risk of bias

for each study. Low risk for bias was defined as no more than two combined “unclear” or non-low (any bias greater than low risk) results in the domain assessment. Medium risk for bias was defined as three to four combined “unclear” or non-low results in the domain assessment. High risk for bias was defined as 5 or more combined “unclear” or non-low results in the domain assessment.

### Role of funding sources

This work was performed without external funding.

## Results

### Literature search

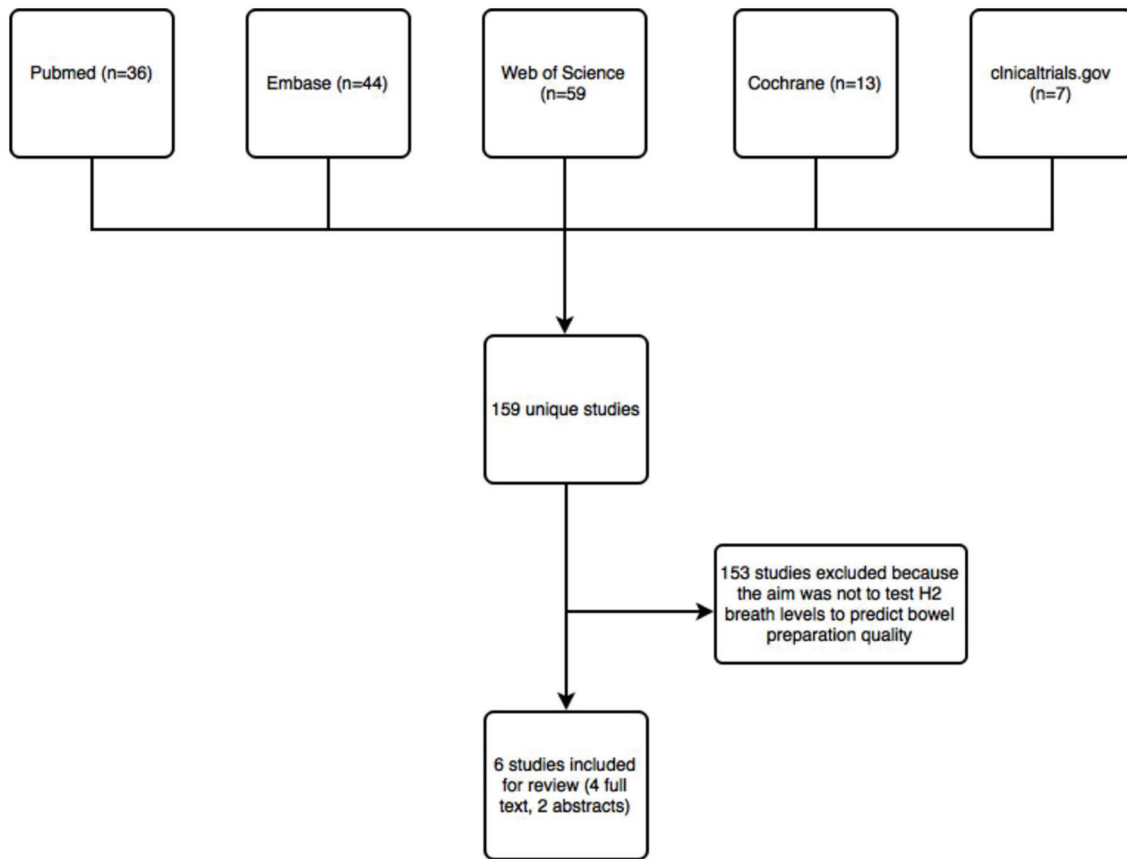
One hundred fifty-nine potentially relevant publications, including abstracts and full-text articles, were identified (Fig. 1). Six unique studies met inclusion criteria, including four from full-text articles and two published only in abstract form. No additional studies were identified after reviewing the references of full-text articles or after searching for articles that subsequently cited any of the six studies.

### Study characteristics

The characteristics of the six studies are shown in Table 1. Altomare et al reported on two distinct studies in a single publication; therefore, two entries are included for this publication [5]. Three studies were performed in the USA, two in Italy and one in Japan. The number of patients analyzed ranged from 61 to 127. Three of the six studies did not report the colonoscopy indication [6, 8, 9]. The remaining studies included colonoscopies that were performed for a variety of indications, including diagnosis, screening and surveillance. A variety of pre-procedure diets were used including carbohydrate-free diet, clear liquids followed by overnight fasting or usual diet followed by overnight fast. Two studies did not comment on dietary changes [8, 9]. Three studies used a prebiotic (inulin, lactulose, FiberCon) in addition to a purgative, with the intention of enhancing the discriminating ability of hydrogen breath levels [5, 7, 9]. Only three studies assessed baseline hydrogen levels [5, 7, 9]. Five of the studies stated which HBT equipment was used, but no studies used the same equipment [5-8].

Significant variation existed in the timing of HBT relative to colonoscopy. For example, Urita et al measured baseline hydrogen levels on the morning of the procedure and then every 15 min until colonoscopy was initiated. In contrast, Altomare et al measured baseline hydrogen levels 1 week prior to colonoscopy and again at 5 min before the bowel preparation and 5 min before the colonoscopy, which allowed for exclusion of H<sub>2</sub> non-producers. Meyer et al did not specify the exact timing of HBT relative to the procedure.

The studies used a variety of bowel preparation regimens.



**Figure 1.** Flow chart of studies identified by literature search.

Four studies used polyethylene glycol (PEG), one study used various preparations, including Fleet's phosphosoda, visicol and golytely, and one study did not state which purgative was used. No study used a standardized, validated bowel preparation scale such as the Ottawa, Aronchick or Boston Bowel Preparation scales [12]. Instead, four studies used excellent/fair/poor and two studies used a 1 - 5 scale, with 1 being the cleanest and 5 being the least clean.

### HBT outcomes

Table 2 describes the HBT outcomes for each study. In five of the six studies, hydrogen breath levels were significantly different between adequately and inadequately prepared patients. Both studies by Altomare et al showed a significant reduction in hydrogen levels after preparation. Mann et al showed a significantly lower hydrogen breath level in the fair-to-excellent preparation group relative to the poor preparation group. One study by Meyer et al showed that hydrogen levels were lower in the adequately prepared group relative to the inadequate group, while a separate study by the same author did not find any difference.

Table 3 lists the suggested hydrogen cutoff level (to discriminate between adequate versus inadequate preparation), whenever reported, as well as the statistical analyses each

study performed. Suggested absolute hydrogen level cutoffs to distinguish adequate from inadequate bowel preparation ranged from 3 to 10 parts per million (ppm). Depending on the cutoff value, sensitivity ranged from 72% to 100% and specificity ranged from 87% to 100%. Positive predictive value (PPV) ranged from 69% to 100%. Negative predictive value (NPV) ranged from 78% to 100%. Due to substantial variation in breath testing methods among studies, a meta-analysis was unable to be performed.

### Study quality and risk of study bias

Table 4 shows the results of the QUADAS-2 assessment. The two studies by Altomare et al were considered as one for the purposes of quality assessment since the methods were identical. The Altomare et al's and Urita et al's studies were scored as low risk for overall bias, and the Mann et al's and Meyer et al's studies were scored as medium risk for overall bias. No study had an individual domain or overall assessment as high risk for bias. The most common reasons for an escalation from low risk to medium risk for bias was lack of clarity in the reported methods. Specific examples include failure to describe whether consecutive patients or a random sample was enrolled, the interval between the colonoscopy and HBT, or whether all enrolled patients were included in the analysis.

Table 1. Study Characteristics

	Altomare group A (PEG only) [5]	Altomare group B (PEG + inulin) [5]	Mann et al (2003) [6]	Urrita et al (2003) [7]	Meyer et al (2001) [9]	Meyer et al (2002) [8]
Study setting and design						
Country	Italy		USA	Japan	USA	USA
Study design	Prospective					
Colonoscopy indication	Screening, surveillance and diagnostic		Unstated	Diagnostic	Unstated	Unstated
Patient selection	Non-consecutive		Unstated	Consecutive	Unstated	
Patient blinded?				Unstated		
Endoscopist blinded?	Yes			Unstated		
Breath tester blinded?	Yes			Unstated		
Exclusion of H <sub>2</sub> non-producers?	Yes		No	Included, analyzed as subgroup	No	No
Inclusion criteria	Signs/symptoms of distal small intestinal diseases, screening or surveillance for colorectal cancer, follow up evaluation of IBD under medical therapy		Unstated	Diagnostic, non-emergent endoscopy	Unstated	Unstated
Exclusion criteria	History of liver, lung, heart, metabolic or neurological disease; lack of compliance, emergency colonoscopy, antibiotic or motility agent 1 month before endoscopy or recent smoking		Unstated	Renal insufficiency, ascites, heart failure, history of abdominal surgery, treatment prokinetics or antibiotics in 6 weeks before endoscopy	Unstated	Unstated
Breath testing protocol						
Baseline (pre-preparation) HBT? If yes, timing	Yes, 5 min before preparation		No	Yes, before starting preparation after fasting	No	Yes, timing unstated
Timing of HBT relative to colonoscopy	5 min before colonoscopy		Unstated	Every 15 min for 4 h before colonoscopy	Unstated	Unstated
Non-hydrogen gases assessed?				No		
Substrate used	None	Inulin	None	Lactulose	None	1/2 pt received 1,250 mg Fibercon the day before colonoscopy
Equipment used	LactoFAN		Bedfont Scientific EC 60 gastrolyzer	TGA-2000, Teramecs	MD-80 breath analyzer	Unstated
Colonoscopy protocol						
Timing of colonoscopy	9 a.m.		Unstated	1 p.m.		Unstated
Bowel preparation scale	Excellent/fair/poor		Excellent/fair/poor	Excellent/fair/poor	1 - 5 (best to worst)	1 - 5 (best to worst)
Definition of "adequate preparation"	Unstated		Unstated	Excellent/fair considered "adequate"	Adequate=1 - 2, inadequate=3 - 5	
Pre-colonoscopy dietary changes	12 h fast before colonoscopy		Clear-liquid diet the day before colonoscopy followed by overnight fast	"Usual diet" the day before procedure, then overnight fast before morning time preparation		Unstated
Purgative used			PEG	PEG	Unstated	Fleet's phosphosoda, visicol or golytely
Single versus split dose preparation	Unstated		Single	Single	Unstated	Unstated

## Group A:

11 patients fasted 1 day before colonoscopy, 31 had carbohydrates without starches 1 day before, 54 pts had no restrictions

## Group B:

No specific dietary changes

**Table 2.** HBT Outcomes by Study

	Altomare group A (PEG only) [5]	Altomare group B (PEG + inulin) [5]	Mann et al. (2003) [6]	Urita et al. (2003) [7]	Meyer et al. (2001) [9]	Meyer et al. (2002) [8]
HBT outcomes	Patients did HBT once (inpatient and outpatient). H <sub>2</sub> level in excellent/fair versus poor was 1.4 ± 0.1 ppm versus 3.5 ± 0.2 ppm (P < 0.001). Patients did HBT twice (inpt only): H <sub>2</sub> level in excellent/fair versus poor was 1.2 ± 0.3 ppm versus 3.3 ± 0.1 ppm (P = 0.005)	Pre-prep to post-prep H <sub>2</sub> levels: 23.8 ± 2.9 ppm versus 2.3 ± 0.3 ppm (P < 0.001).	H <sub>2</sub> levels were lower in the fair-to-excellent prep group (2.2 ± 0.2 ppm) relative to the poor prep group (14.5 ± 1.5 ppm, P < 0.005)	No difference in baseline H <sub>2</sub> levels between the adequate and inadequate group At 90 min into preparation, the H <sub>2</sub> level in the adequate group (18 ppm) was lower than the inadequate group (32 ppm) but without a reported P value At 240 min into preparation, the H <sub>2</sub> level in the adequate group (1.6 ppm) was significantly lower than in the inadequate group (43.4 ppm, P < 0.01)	H <sub>2</sub> levels were lower in the adequately prepared group (1.56 ppm) relative to the inadequately prepared group (2.11 ppm, P < 0.05)	No difference between baseline H <sub>2</sub> levels and post-prep H <sub>2</sub> levels in the adequately prepared group relative to the inadequately prepared group

**Discussion**

Inadequate bowel preparation has been a persistent problem in endoscopy units despite incremental improvements from better formulations and timed dosing of bowel purgatives [1]. The clinical and economic harms associated with this problem are legion: missed cancers, repeat procedures, excess health system cost, patient inconvenience and risk, and endoscopy unit inefficiency [13-15]. A strategy that could detect patients who have had inadequate bowel preparation before the colonoscopy starts could stem many of the harms associated with inadequate bowel preparation. We reviewed all studies to date that have examined the performance of HBT for this purpose. We found that five of six studies demonstrated significant differences in hydrogen breath levels between adequately and inadequately prepared patients. Furthermore, multiple different breath testing protocols, involving the use of carbohydrate substrates, or none at all, were used successfully. Our systematic review suggests the future promise of hydrogen breath testing for detecting inadequate bowel preparation. With future studies clarifying a dominant strategy, the use of hydrogen breath testing may represent a possible paradigm shift for how endoscopy units identify inadequate bowel preparation prior to sedation and instrumentation.

Previous attempts at identifying patients with inadequate bowel preparation before procedure start have been unsuccessful. While appealing because of low cost, low risk and ease of use, the appearance of fecal effluent and patient self-report have proven unreliable predictors of bowel preparation quality [16, 17]. Alternatively, the US Multi-Society Task Force recommends that preliminary assessment of preparation quality be made endoscopically in the rectosigmoid colon with termination of procedures in which the bowel preparation is inadequate to detect polyps > 5 mm [18]. However, endoscopic assessment of bowel preparation still incurs substantial expense and (typically) sedation risk simply to make a determination of preparation adequacy. Several clinical prediction models have been developed to identify patients who are high risk for inadequate bowel preparation [19, 20]. However, these are more appropriately used to tailor the selection of the bowel preparation regimen, not for post-preparation assessment of adequacy.

While the results of our review suggest that pre-colonoscopy HBT is extremely promising, additional, more robust studies are needed to confirm the accuracy and feasibility of this testing strategy. Specifically, future studies should use rigorous methods, including endoscopist blinding and standardized bowel preparation scales. Future research into pre-colonoscopy breath testing should also be mindful of implementation strategies. For ease of use in practice, breath testing would ideally be done at a single time point and without the need for a carbohydrate substrate. The studies reviewed suggest that this is possible, which should be confirmed in the future. It will also be important to consider where and how breath testing can be integrated into current pre-colonoscopy practices. If breath testing is done at the time of patient arrival in the endoscopy unit, there will need to be protocols for how to administer additional purgative or reschedule the patients for another time. Breath testing at home prior to departure for

**Table 3.** Statistical Analysis and Proposed Hydrogen Level Cutoffs for Poor Bowel Preparation

	Altomare group A (PEG only) [5]	Altomare group B (PEG + inulin) [5]	Mann et al (2003) [6]	Urita et al (2003) [7]	Meyer et al (2001) [9]	Meyer et al (2002) [8]
H <sub>2</sub> cutoff value suggested (ppm)	3	3	5	10 at 90 and 240 min into prep ingestion	Unstated	N/a since no difference was found
Sensitivity (%)	72	83	96.7	100		
Specificity (%)	93	87	87.5	100		
NPV (%)	93	93	77.8	100		
PPV (%)	72	69	98.3	100		
AUROC/c-statistic	Not available	0.93	Not available	Not available		

the endoscopy unit has appeal, but it is unclear how this could be carried out feasibly.

Our review has several strengths and limitations. First, we used a comprehensive search strategy that included both full-text studies as well as abstracts. Additionally, we examined and reported breath testing protocols in great detail, which likely contributed to observed differences in results among studies

and will be useful in guiding future studies of this topic. A notable limitation is that multiple studies were unclear in their patient selection process and endoscopist blinding. Another limitation of the review is that meta-analysis with summary estimates of results could not be conducted given the significant heterogeneity of study designs. Lastly, our results are subject to the same threats to validity that exist in the constituent

**Table 4.** QUADAS-2 [10] Assessment

	Altomare et al (both studies) [5]	Mann et al (2003) [6]	Urita et al (2003) [7]	Meyer et al (2001) [9]	Meyer et al (2002) [8]
Overall QUADAS-2 rating	Low risk of bias	Medium risk of bias	Low risk of bias	Medium risk of bias	Medium risk of bias
Domain 1 (patient selection)	Unclear if selection introduced bias; overall low concern that included patients did not match the review question	Unclear if selection introduced bias; overall low concern that included patients did not match the review question	Low risk of selection introducing bias; overall low concern that included patients did not match the review question	Unclear if selection introduced bias; overall low concern that included patients did not match the review question	Unclear if selection introduced bias; overall low concern that included patients did not match the review question
Domain 2 (index test)	Low risk that conduction or interpretation of the index test could have introduced bias; low concern that the index test, its conduct or interpretation differed from the review question	Low risk that conduction or interpretation of the index test could have introduced bias; low concern that the index test, its conduct or interpretation differed from the review question	Low risk that conduction or interpretation of the index test could have introduced bias; low concern that the index test, its conduct or interpretation differed from the review question	Low risk that conduction or interpretation of the index test could have introduced bias; low concern that the index test, its conduct or interpretation differed from the review question	Low risk that conduction or interpretation of the index test could have introduced bias; unclear concern that the index test, its conduct or interpretation differed from the review question
Domain 3 (reference standard)	Low risk that the reference standard, its conduct or interpretation could have introduced bias; low concern regarding the target condition matching the review question	Unclear risk that the reference standard, its conduct or interpretation could have introduced bias; low concern regarding the target condition matching the review question	Unclear risk that the reference standard, its conduct or interpretation could have introduced bias; low concern regarding the target condition matching the review question	Unclear risk that the reference standard, its conduct or interpretation could have introduced bias; low concern regarding the target condition matching the review question	Unclear risk that the reference standard, its conduct or interpretation could have introduced bias; low concern regarding the target condition matching the review question
Domain 4 (flow and timing)	Low risk that patient flow introduced bias	Unclear risk that patient flow introduced bias	Low risk that patient flow introduced bias	Unclear risk that patient flow introduced bias	Unclear risk that patient flow introduced bias

studies.

In conclusion, our systematic review suggests that pre-colonoscopy hydrogen breath testing has high discriminant ability to differentiate patients with adequate versus inadequate bowel preparation, and that a range of carbohydrate substrates may be used, or even none at all. Further research in this area could potentially lead to a more proactive, effective and safer means to ensure every patient achieves adequate bowel preparation.

## Acknowledgments

We acknowledge Marisa Conte, the Assistant Director of Research and Informatics Unit for the Taubman Health Sciences Library at the University of Michigan. She was instrumental in creating a comprehensive search strategy.

## Author Contributions

Dr. Sondhi is the guarantor of the article and takes responsibility for the integrity of the work as a whole, from inception to published article. Drs. Sondhi and Kurlander and performed literature review and data extraction. Drs. Sondhi and Kurlander wrote the manuscript. All authors contributed to the editing of the manuscript. Dr. Saini designed the project and supervised it as the senior mentor. All authors approved the final version of the manuscript.

## Conflict of Interest

The authors declare no conflict of interest.

## Financial Support

No external funding was provided for this study.

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