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Original Article

Positive impact of a diagnostic stewardship intervention on syndromic panel ordering practices and inappropriate *C. difficile* treatment

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Abstract

Objective: Multiplex polymerase chain reaction (PCR) panels for stool testing may be used to diagnose *Clostridioides difficile*, which can circumvent more appropriate targeted *C. difficile* testing, resulting in treatment of incidentally detected colonization. We sought to reduce *C. difficile* diagnosis via a gastrointestinal pathogen panel (GIPP).

Design: Quasi-experimental, pre/post, retrospective cohort study from January 1, 2022, to January 31, 2024.

Setting: Mayo Clinic Arizona—a single academic medical center and associated clinics.

Patients: Adult patients receiving *C. difficile* testing and/or treatment.

Methods: Preferred *C. difficile* testing consisted of glutamate dehydrogenase and toxin antigen immunoassay, followed by toxin gene testing for discrepant results. The GIPP contained 22 targets during the baseline period with *C. difficile* removed during the postintervention period. Surveys were provided to provider and nursing groups, separately, to identify *C. difficile* ordering practices and knowledge gaps.

Results: At baseline, from January 1, 2022, to January 31, 2023, 2,772 GIPPs were completed for 2,307 unique patients (~7 per day), primarily for outpatients (1,805 of 2,772, 65%). The most common positive target was *C. difficile* (517 of 1,018, 51%), which resulted in treatment for *C. difficile* infection in 94.9% (337 of 355) of cases. Following GIPP *C. difficile* target removal, GIPP orders decreased from 3.23 to 2.7 per 1,000 patient visits ($P < .001$). Prescribing of *C. difficile* treatments decreased in the postintervention period in inpatient and outpatient settings. There were no cases of delayed *C. difficile* diagnosis during the postintervention period.

Conclusions: Removing *C. difficile* from the GIPP resulted in effective diagnostic and antimicrobial stewardship without resulting in delayed diagnoses.

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Background

Multiplex molecular panels have rapidly replaced many conventional testing methods due to their speed, analytical sensitivity, and convenient workflows. The replacement of traditional stool culture with gastrointestinal (GI) pathogen panels (GIPPs) results in faster time to pathogen-directed therapy, discontinuation of empiric therapy, reduced inpatient isolation time frames, and lower 30-day gastroenteritis-related hospitalization risk.[1–5] Conversely, the broad inclusion of several targets that may detect colonization rather than true infection is a significant limitation of certain GIPPs, emphasizing the need for diagnostic stewardship.[6] One of the most controversial targets is *Clostridioides difficile*. *C. difficile* is a common cause of healthcare-associated infections with high morbidity and mortality if left untreated, but it is also a frequent colonizer of the GI tract with up to 18% prevalence in hospital settings and up to 51% prevalence in long-term care facilities.[7,8] Detection of *C. difficile* colonization can result in unnecessary treatment, affecting an individual patient's gut health via microbiome disruption.[9]

At our institution, the preferred testing for *C. difficile* infection (CDI) uses a paired toxin antigen and glutamate dehydrogenase (GDH) enzyme lateral flow assay, which reflexes to a toxin A/B molecular test if only 1 antigen is positive. A molecular GIPP, which tests for 22 targets including *C. difficile*, is also orderable without restriction except for inpatients over 72 hours postadmission.

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The GIPP cannot differentiate *C. difficile* colonization from infection. Care process models are in place for both testing methods to guide appropriate ordering based on patients' symptoms and risk factors. However, a previously published, limited review of our internal data indicated that *C. difficile* is the most common target identified on our GIPP and that the GIPP is ordered more frequently than our preferred *C. difficile* test, suggesting inappropriate utilization.[10] We therefore set out to evaluate the drivers behind ordering practices as well as identify opportunities to steward the use of the GIPP via the removal of the *C. difficile* target, without causing delayed CDI diagnosis.

Methods

This was a single-center, quasi-experimental, pre/post, retrospective cohort study conducted as routine quality improvement, for which Institutional Review Board approval was waived. All patients who received any *C. difficile* testing and/or treatments at our institution over the study period were eligible for inclusion.

Laboratory testing

At our institution, all inpatient and emergency department stool samples are submitted unpreserved in sterile containers. Stool samples from outpatient sites are placed into liquid preservatives, which may affect the ability to assess stool consistency. Stool samples submitted for standalone *C. difficile* testing or GIPP were evaluated by laboratory personnel for consistency and had testing canceled if they did not take the shape of the container or resulted in the stabilization of a small wooden dowel upon placement into the container (aka "stick test"). *C. difficile* testing was performed using the FDA-cleared *C. diff* Quik Chek Complete (Tech Lab, Blacksburg, VA) following the manufacturer's instructions for use.[11] Samples that tested positive for only 1 antigen were reflexed to the Xpert *C. difficile* assay (Cepheid, Sunnyvale, CA).

Panel testing was performed using the FilmArray GIPP (BioFire Diagnostics, bioMerieux, Salt Lake City, UT). Ordering of the GIPP was restricted via the electronic health record to the first 72 hours postadmission. Orders after that time required consultation and ordering by an infectious diseases (ID) provider.

Study design and interventions

We convened a multidisciplinary team to evaluate GIPP misuse for the diagnosis of *C. difficile*. Two surveys were developed by the team: 1 for nursing and 1 for providers (see Supplementary Materials). The provider survey asked questions regarding indications for their GIPP ordering and knowledge regarding *C. difficile* and GIPP testing. The nursing survey focused on appropriate patient signs and symptoms and stool consistency for GIPP and *C. difficile* testing orders. Surveys were distributed by team leads to the provider groups and inpatient/ED/outpatient GI clinic nurses as part of a formal gap analysis.

Ultimately, the decision was made to remove the *C. difficile* target from the GIPP as the primary intervention. A software update provided by BioFire was installed in February 2023 to mask the *C. difficile* target from being visible to the laboratory staff and mask reporting. One primary concern with *C. difficile* masking was the potential harm to patients due to the lack of awareness, resulting in delays in *C. difficile* testing and CDI diagnosis. The team discussed behavioral and operational strategies to mitigate the risk of delayed diagnosis. The primary interventions included alerts in the electronic health record (EHR) at the time of ordering to clarify that the GIPP no longer includes the *C. difficile* target and prompts for either 1) additional testing via the preferred *C. difficile test* or 2) replacement of the GIPP with the preferred *C. difficile* test (Supplemental Figure 1a). Alerts on the GIPP result were also created in the laboratory information system to autogenerate a result for the *C. difficile* target to state "not tested" (Supplemental Figure 1b). For a burn-in period of 2 months, abnormal flagging was generated in the EHR on all GIPP results, even when negative, to prompt review of the full results display including *C. difficile* "not performed," such that it would not be missed by an assumption that the full panel was negative.

The study included a baseline period of January 1, 2022–January 31, 2023, a washout month of February 2023, and a postintervention period of March 1, 2023–January 31, 2024. *C. difficile* test and GIPP results were recorded. During the postintervention period, every inpatient case of *C. difficile* more than 72 hours after admission was reviewed by infection control to determine if any were the result of delayed diagnosis due to testing changes. All patients with a new diagnosis of toxic megacolon (ICD-10 code K59.31) were recorded.

Targeted education was provided by an ID physician to top GIPP ordering groups between November 2022 and January 2023, which included family medicine (November 2, 2022), internal medicine residents (November 16, 2022), hospital internal medicine (December 16, 2022) and emergency medicine (January 4, 2023). These sessions highlighted the differences between various *C. difficile* diagnostics and notified providers of the upcoming removal of *C. difficile* from the GIPP. Education was also broadly disseminated to all practice areas via electronic memorandums.

Data sources and statistical analysis

A hypothetical reduction in patient charges for GIPP testing was calculated using the 2024 quarter 1 Clinical Laboratory Fee Schedule rate for our GIPP panel, GDH, and toxin EIA and targeted *C. difficile* PCR (rates of \$416.78, \$11.98 × 2 and \$37.27, respectively; https://www.cms.gov/license/ama?file=/files/zip/24CLABQ1.zip, accessed July 2, 2024). The change in the rate of GIPP orders per patient encounter between the baseline and postintervention periods was calculated, multiplied by the total patient encounters for the postintervention period, and multiplied by the fee to produce a hypothetical charge reduction. The same number of targeted C. *difficile* antigen tests and a subset of tests reflexed to targeted PCR due to indeterminate results were multiplied by the fee and subtracted from the hypothetical reduction. To investigate the impact of *C. difficile* masking on unnecessary *C. difficile* treatment, we analyzed outpatient prescriptions of enteral vancomycin or fidaxomicin, normalizing the number of prescriptions per 1,000 outpatient visits in each study period. Inpatient data were assessed using days of therapy (DOT) per 1,000 days present (DP) and only included orders with an indication of CDI, excluding prophylaxis orders. GIPP and standalone *C. difficile* tests were aggregated by month and normalized to every 1,000 patient visits. Baseline and post-intervention results were compared using χ^2 test for categorical data and the Student *t* test to compare means. All analyses were performed in IBM SPSS Statistics (Version 28.0.0.0).

Results

During the baseline period, from January 1, 2022, to January 31, 2023, 2,772 GIPPs were completed for 2,307 unique patients

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(Table 1, ~ 7 per day). The majority were ordered for outpatients (Supplemental Table 1, 1,805 of 2,772, 65%). During this period, the most common positive target was *C. difficile* (Table 1, 517 of 1,018, 51%), which resulted in treatment for CDI in 94.9% (337 of 355) of cases. During this same period, only 763 orders were placed for the preferred *C. difficile* testing method, with 55 (7.2%) positive.

As a follow-up to this baseline data and observations, a survey was created to better understand the GIPP and *C. difficile* ordering habits of providers. This survey (see methods) was distributed to 6 providers who were then asked to cascade to their respective groups. From this distribution pool, which was not quantified, 49 responded. The respondents included 28 (57%) from hospital internal medicine, 14 (29%) from emergency medicine, and 7 (14%) from gastroenterology, the most common services to order the GIPP (Supplemental Table 1). Most (86%) responded that they ordered the GIPP at least monthly. The most frequent reason for GIPP panel ordering was testing for "other bacterial causes" (41 of 49, 83.7%, Supplemental Figure 2) followed by testing for *C. difficile* (28 of 49, 57%). A free-text field was available for additional comments, in which 2 providers stated that GI consult recommendation is a common influence to place a GIPP order. Importantly, only half of provider respondents answered correctly that the GIPP positivity is higher compared to standalone *C. difficile* testing; incorrect answers included 16% that stated the GIPP tests for the presence of free toxin, 2.5% that a positive *C. difficile* on the GIPP should never be considered colonization, and 2.5% that a GIPP is appropriate to send as a primary *C. difficile* test (Supplemental Figure 3). Similarly, more than half (25 of 49, 51%) of respondents did not understand when a repeat panel could be indicated, including 16% who responded repeat testing would be appropriate to verify the validity of 3 or more positive targets, a common finding with the GIPP (Supplemental Figure 4).

A total of 275 nurses responded to the nursing survey, of whom 239 (87%) indicated they were familiar with the stool types suitable for GIPP and *C. difficile* testing, and although the majority were comfortable with how to manage a situation in which *C. difficile* testing was not appropriate, 33% were not. In free-text comments, 10% noted there was provider insistence to send a GIPP despite nursing pushback based on patient symptoms.

There was a significant reduction in GIPP panel ordering from 3.23 to 2.7 orders per 1,000 patient visits (Figure 1 and Table 1, $P <$ .001) and an increase in the preferred *C. difficile* test orders from 764 to 1,273 orders comparing baseline and postintervention periods, respectively (Figure 1 and Table 1). Although the positivity rate for the *C. difficile* target on the GIPP expectedly dropped from 18.7% to zero between the study periods, the positivity rate for the preferred *C. difficile* test did not drop significantly (7.2% vs 5.5%, *P* value not significant), suggesting the larger denominator of testing orders did not have an impact. Regardless, the reduction in GIPP orders was partially replaced with the preferred *C. difficile* test, which was the desired outcome. Based on the 2024 clinical laboratory fee schedule, a reduction of 0.53 GIPP per 1,000 patient visits would have saved a hypothetical 423 unnecessary GIPP orders, which were replaced by targeted *C. difficile* testing, of which 12.05% would have reflexed to a targeted PCR due to indeterminate results, resulting in a hypothetical savings of $164,337.85 in charges during the 11-month post-intervention period.

Outpatient CDI prescriptions declined over the study, with a mean of 2.36 per 1,000 outpatient visits in the baseline period and 1.81 per 1,000 outpatient visits in the postintervention period (Table 1, $P = <.001$). For the inpatient setting, DOT per 1,000 DP decreased from 13.77 in the baseline period to 10.58 in the postintervention period, though the reduction did not meet statistical significance ($P = .051$). A total of 36 inpatient records with *C. difficile* detected more than 72 hours after admission were reviewed. None represented delayed testing or diagnosis in the postintervention period. ICD-10 diagnosis codes for toxic megacolon were also compared between the baseline and post-intervention periods with 5 cases in the baseline and 3 cases in the postintervention period. Zero of these 3 cases in the post-intervention period were associated with CDI, and no testing for infectious pathogens was pursued in any of these cases, including GIPP and targeted *C. difficile* testing.

Discussion

The goal of this study was to improve the accurate diagnosis of CDI and reduce unnecessary treatment of *C. difficile* colonization at our institution. In the context of chemotherapeutic agents, laxatives, or irritable bowel flares, the finding of *C. difficile* may be inappropriately interpreted as an infection. Our team hypothesized that the inappropriate use of the GIPP led to increased detection of *C. difficile* colonization and potentially harmful treatment. Survey feedback from ordering providers and nursing colleagues strengthened this hypothesis. As a result, the decision was made to mask the *C. difficile* target from the GIPP, via a recent manufacturer software update, while simultaneously mitigating any potential harm due to delayed CDI diagnosis. Through a multidisciplinary approach to diagnostic stewardship, education, and leveraging clinical decision support tools within the EHR, we found a significant reduction in total GIPP orders concomitant with masking of the *C. difficile* target, a significant increase in targeted *C. difficile* testing orders, and reduction in outpatient prescriptions for CDI treatment. Taken together, these data suggest that such an approach could be translatable to other institutions to improve the accuracy of CDI diagnosis and limit treatment to true CDI.

One of the most important considerations prior to *C. difficile* target masking on the GIPP was the risk of patient harm. A behavioral approach was undertaken to identify opportunities for success. The changes to the ordering display in the EHR ensured that ordering providers knew at ordering that *C. difficile* was no longer included on the GIPP and allowed for selecting targeted *C. difficile* testing in the same field. Similarly, changes were made on the reporting end to indicate that *C. difficile* is no longer a target on the panel. An abnormal result alert flag was also added to all tests with negative results, for a burn-in period, to draw attention to all results, because a negative result in the EHR does not require a review of individual panel targets. For the 11-month post-intervention study period, there were no apparent cases of CDI that were the result of a delayed diagnosis due to target masking. This finding differs from a recent study that retrospectively evaluated the impact of *C. difficile* target masking on their GIPP over a 1-year period, suggesting suppression resulted in several cases of definitive delayed CDI diagnosis and treatment.[12] Interestingly, the study site used a targeted *C. difficile* PCR as their preferred test, and there was no explanation as to why cases with delayed diagnosis did not have that test ordered because the *C. difficile* masking was not a recent intervention. Further, although the target was masked from the EHR, it was visible on the laboratory report and was reviewed daily by an ID physician for potential reporting. It was also unclear why that intervention was unsuccessful. In our study, tremendous emphasis was placed on education around the

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Table 1. Outcomes baseline and postintervention following education and removal of *C. difficile* target from GIPP

Outcomes	Baseline	Postintervention	*P* value
GIPP orders/1,000 visits (SD)	3.23 (0.35)	2.70 (0.27)	<.001
Any target detected on GIPP[a](%)	1,018 (36.7%)	532 (24.7%)	<.001
Adenovirus	11 (1.1%)	6 (1.1%)	
Astrovirus	17 (1.7%)	25 (4.7%)	
Clostridioides difficile	517 (50.8%)	Not tested	
Campylobacter	46 (4.5)	49 (9.2%)	
Cryptosporidium	11 (1.1%)	7 (1.3%)	
Cyclospora	2 (0.2%)	11 (2.1%)	
Entamoeba histolytica	2 (0.2%)	1 (0.2%)	
Enteroaggregative *Escherichia coli*	75 (7.4%)	58 (10.9%)	
Enteropathogenic *E. coli*	159 (15.6%)	118 (22.2%)	
Enterotoxigenic *E. coli*	45 (4.4%)	33 (6.2%)	
Giardia	14 (1.4%)	7 (1.3%)	
Norovirus	182 (17.9%)	197 (37%)	
Plesiomonas shigelloides	3 (0.29%)	3 (0.6%)	
Rotavirus	48 (4.7%)	32 (6.0%)	
Salmonella species	29 (2.9%)	29 (5.5%)	
Sapovirus	23 (2.3%)	36 (6.8%)	
Shiga toxin-producing *E. coli*	16 (2.6%)	21 (4.0%)	
Shigella/enteroinvasive *E. coli*	23 (2.3%)	12 (2.3%)	
Vibrio cholerae	1 (0.1%)	0 (0%)	
Vibrio species	5 (0.5%)	0 (0%)	
Yersinia species	17 (1.7%)	12 (2.3%)	
Standalone *C. difficile* tests/1,000 visits (SD)	0.92 (0.16)	3.06 (0.25)	<.001
Positive standalone *C. difficile* tests/# ordered (%)	55/763 (7.2%)	70/1273(5.5%)	NS
Outpatient *C. difficile* prescriptions/1,000 outpatient visits (SD)[b]	2.36 (0.34)	1.81 (0.37)	<.001
Inpatient *C. difficile* antibiotic DOT/1,000 DP	13.77	10.58	NS ($P = .051$)

Note. GIPP, gastrointestinal pathogen panel; DOT, days of therapy; DP, days present.
[a]Multiple targets may be positive per panel.
[b]Fidaxomicin or oral vancomycin.

change in target masking as well as our preferred testing algorithm for CDI, including point of ordering education in the EHR. These components are likely why our intervention resulted in no evidence of delays in CDI diagnosis.

Our study has potential limitations. First, it was performed in a single tertiary care academic medical center and thus our findings may not be broadly generalizable. For example, our center in Phoenix has led the United States in solid organ transplants since 2020 and manages a high proportion of immunocompromised patients with extensive health care and antibiotic exposures, which are risk factors for *C. difficile* colonization and CDI. Another limitation is the implementation of changes in the EHR and laboratory information systems in our study, which may be limited in some centers. Additional study limitations include the analysis of only inpatients testing positive for *C. difficile* more than 72 hours after admission as a metric for potential harm in the post-intervention period. It is possible that some outpatients had a delayed diagnosis in the postintervention period due to *C. difficile* masking on the GIPP and either had targeted *C. difficile* testing within 72 hours of admission, testing in the outpatient setting, or admission to a different hospital for CDI. There is also intense debate as to the most appropriate primary test method for CDI diagnosis. Although a review of the pros and cons of testing methods is beyond the scope of this study, several reviews on this topic are available.[13–15] It is important to point out that during the postintervention period, there were zero cases of CDI-associated toxic megacolon identified via ICD-10 code review, suggesting our approach is not insensitive for CDI that can lead to severe disease. This study investigated the impacts of a single intervention, masking the *C. difficile* target, while other interventions, such as hard stops for repeat GIPP testing during a specified time frame, may also have reduced unnecessary ordering based on survey feedback. Additional interventions should be studied.

Although syndromic molecular panels have created substantial advances in the speed and sensitivity of ID diagnoses, the broad inclusion of targets for which individual patients may not have risk factors is a well-recognized limitation. Recently, a Medicare Administrative Contractor group, which covers more than half of

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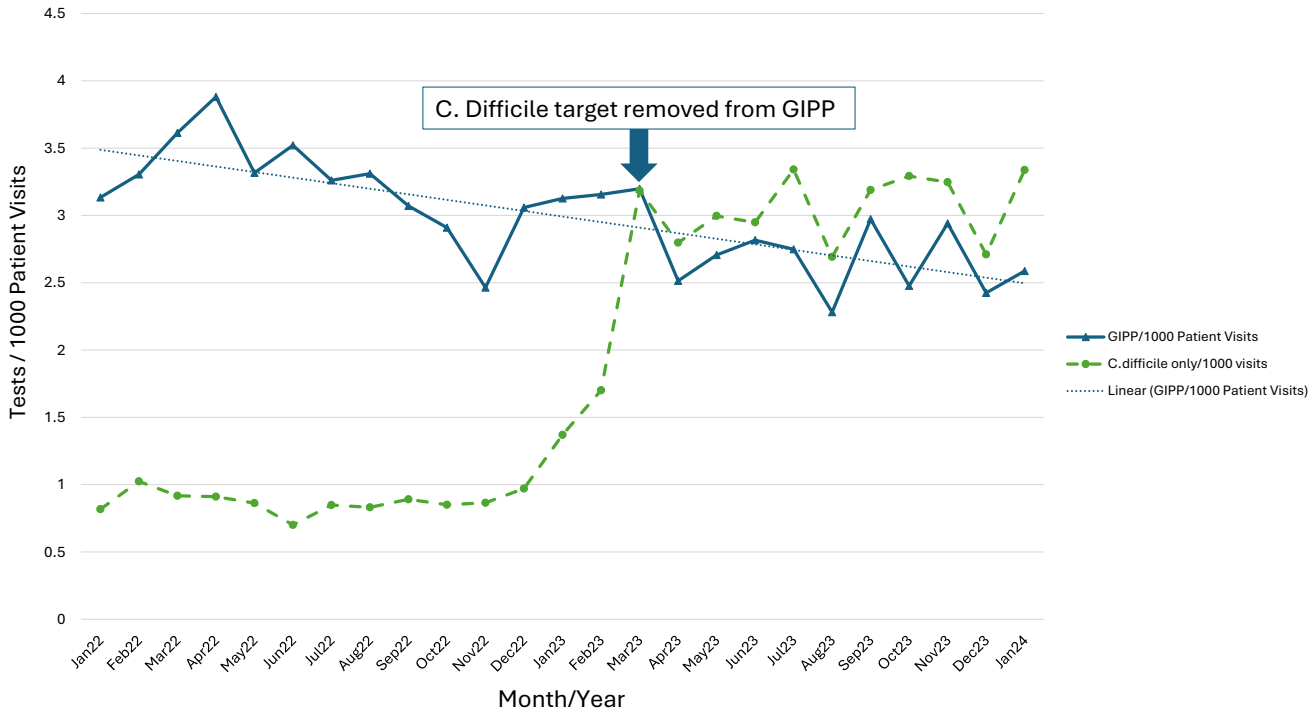

Figure 1. Gastrointestinal pathogen panel (GIPP) and standalone *Clostridioides difficile* testing orders per 1,000 patient visits over time. The rate of GIPP orders per 1,000 patient visits is displayed in solid blue, and the rate of *C. difficile*-only orders per 1,000 patient visits is displayed in dashed green, per month. The x-axis represents each month during the study time frame. The time at which *C. difficile* was removed from the GIPP is indicated with the large blue arrow. Linear regression analysis (blue dotted line) shows a negative relationship between GIPP orders per 1,000 patient visits and time over the study period.

the United States, significantly restricted coverage of large syndromic panels due to the presence of targets that are not necessarily clinically indicated for an individual patient.[16] In addition, positive results for targets that may represent false detections or colonization can lead to unnecessary treatment and additional workup, possibly leading to delays in determining the true etiology of disease. As a result, many professional societies and institutions are recommending stewardship interventions to ensure the right test is being performed on the right sample at the right time.[17–19] Laboratory testing for *C. difficile* is one of the most common targets of diagnostic stewardship interventions, with many advocating that it should be routinely suppressed on GIPPs to drive more appropriate targeted testing.[20,21] This study provides a roadmap to the successful suppression of *C. difficile* testing on GIPP, a reduction in inappropriate GIPP ordering, and unnecessary treatment without causing patient harm.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2024.180.

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Competing interests. All authors have acknowledged that they have no conflicts of interest to declare.

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