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Impact of Gastrointestinal Panel Implementation on Health Care Utilization and Outcomes

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ABSTRACT PCR-based multiplex gastrointestinal (GI) pathogen panels have started to replace stool culture and ova and parasite exam as a rapid and accurate means of diagnosing acute gastroenteritis. However, there are limited data on the impact of panel testing on patient outcomes. The objective of this study was to evaluate the management and health care utilization of patients following GI panel compared with conventional stool testing. We performed a retrospective comparative analysis of 9,402 patients who underwent testing with the FilmArray GI panel from March 2015 through May 2017 and 5,986 patients who underwent conventional stool testing from December 2012 through February 2015. GI panel was positive in 2,746 exams (29.2%) compared with 246 exams (4.1%) with conventional testing. Within 30 days following stool testing, compared with patients who received a conventional stool test, patients who received a GI panel were less likely to undergo any endoscopic procedure (8.4% GI panel versus 9.6% stool culture, $P = 0.008$) or any abdominal radiology (29.4% GI panel versus 31.7%, $P = 0.002$). Within 14 days following stool testing, patients who received a GI panel were less likely to be prescribed any antibiotic (36.2% GI panel versus 40.9%, $P < 0.001$). The implementation of multiplex PCR stool testing was associated with a reduction in the utilization of endoscopy, abdominal radiology, and antibiotic prescribing.

KEYWORDS diagnostics, gastrointestinal infection, multiplex PCR

Gastroenteritis is a major cause of morbidity and mortality worldwide (1, 2). The Centers for Disease Control and Prevention estimate nearly 48 million cases annually in the United States, accounting for a large number of hospitalizations and outpatient visits and significant direct and indirect costs (2, 3). Acute diarrheal illness may occur due to infection with viral, bacterial, or parasitic pathogens, typically resulting in diarrhea associated with enteric symptoms, such as abdominal pain and/or cramping, fever, malaise, bloody stools, nausea, and vomiting, that generally lasts for less than 14 days (1, 4). Although most acute enteric infections are self-limited, such infections may result in more severe illness requiring hospitalization. In addition, sequelae can include Guillain-Barré syndrome, reactive arthritis, postinfection irritable bowel syndrome, postinfection malabsorption syndrome, or hemolytic uremic syndrome (4).

Identifying an infectious agent may assist in decision-making regarding treatment, patient isolation, management, and further investigations (5–7). From a public health perspective, the identification of a pathogen is also an important consideration in evaluating outbreaks due to foodborne or seasonal illness (2, 8). Recently, many clinical laboratories have adopted multiplex-PCR-based gastrointestinal pathogen panels as a rapid and accurate means of diagnosing acute gastroenteritis (4, 9, 10). These assays

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allow for the identification of specific organisms not previously and readily diagnosable by the clinician. Clinical accuracy studies have demonstrated the superiority of multiplex PCR stool testing in producing a greater number of pathogen-positive findings than conventional testing (11, 12).

Despite the recent and widespread uptake of multiplex PCR stool testing in clinical practice, there is considerable uncertainty regarding the clinical importance of additional pathogen-positive findings and the utilization impact of such testing on the management of patients. In the present study, focusing on endoscopy, abdominal radiology, and antibiotic utilization, we sought to compare the management of patients following conventional stool testing compared with the management of patients following multiplex PCR stool testing.

MATERIALS AND METHODS

Study population and variables. We performed a cross-sectional study using the electronic medical records of patients at New York Presbyterian-Columbia University Medical Center, a quaternary care institution in New York City that serves patients from the surrounding urban area, the tristate region (New York, New Jersey, and Connecticut), as well as people seeking care from more distant regions. In March of 2015, our institution switched from stool testing using culture to stool testing using a gastrointestinal (GI) panel (i.e., after this date, culture was no longer available). We identified all outpatients and inpatients who underwent stool testing with a FilmArray GI pathogen panel (BioFire Diagnostics, Salt Lake City, UT) during the 26-month period spanning March 31, 2015 through May 9, 2017. We then identified all outpatients and inpatients who underwent conventional stool testing with a stool culture with and without an ova and parasites exam or enzyme immunoassay (EIA) for rotavirus and adenovirus 40/41 during the 26-month period spanning December 1, 2012 to March 30, 2015.

We recorded the following values from the medical record: stool test, date of stool test, stool-testing results, date of birth, zip code, place of PCR test (e.g., emergency department, outpatient visit, inpatient hospitalization, and endoscopy), sex, race, ethnicity, length of stay (LOS) if inpatient, and presence of inflammatory bowel disease (IBD), celiac disease, or HIV using International Classification of Diseases (ICD) coding.

We then collected the following utilization data from the medical record: any endoscopic procedure, including esophagogastroduodenoscopy (EGD), sigmoidoscopy, enteroscopy, and/or colonoscopy, in the 30 days following a stool test; any emergency room visit and/or hospitalization in the 30 days following a stool test; any abdominal radiology, including abdominal X ray (AXR), barium enema, computed tomography (CT) abdomen and/or pelvis, CT enterography, esophagram, hepatobiliary scintigraphy (HIDA), magnetic resonance (MR) abdomen and/or pelvis, MR enterography, upper gastrointestinal (GI) series, and/or abdominal ultrasound, in the 30 days following a stool test; other common radiology, including chest X ray (CXR) or CT chest, in the 30 days following a stool test; and any antibiotic prescribing, including metronidazole, penicillins, cephalosporins, carbapenems, aminoglycosides, quinolones, macrolides, and/or tetracyclines, in the 14 days following a stool test.

All repeat stool tests were excluded. A random sample of 25 patients was assessed to confirm that identified records had correct diagnostic codes, stool test dates, and results. Of those sampled patients, all patients were correctly classified.

Enteric pathogen testing. The GI panel is capable of the simultaneous detection and identification of nucleic acids from multiple bacteria, viruses, and parasites directly from stool samples in Cary Blair transport medium. The test run time is approximately 1 hour and has a clinical sensitivity and specificity of 94.5% to 100% for all targets.(4, 13) The GI panel tests for 22 analytes in stool, namely, 13 bacteria, 5 viruses, and 4 parasites, including *Campylobacter jejuni*, *C. coli*, *C. upsaliensis*, *Clostridioides* (*Clostridium*) *difficile* (toxin A/B), *Plesiomonas shigelloides*, *Salmonella* spp, *Yersinia enterocolitica*, *Vibrio parahaemolyticus, V. vulnificus*, V. *cholerae*, enteroaggregative *Escherichia coli* (EAEC), enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), Shiga-like toxin-producing *E. coli* (STEC), *E. coli* O157, *Shigella*/enteroinvasive *E. coli* (EIEC), *Cryptosporidium* spp., *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Giardia lamblia*, adenovirus (AdV) F40/41, astrovirus, norovirus GI/GII, rotavirus A, and sapovirus (I, II, IV, and V). In our institution, an alternative PCR test is utilized for *Clostridoides* (*Clostridium*) *difficile* (Xpert *C. difficile*; Cepheid, Sunnyvale, CA), and as such, these results are not reported with the GI panel and were not examined in this study. Patients with a positive *C. difficile* PCR within 7 days of a GI panel or stool culture were excluded from the study. GI panel testing was repeated for rare targets (*Plesiomonas shigelloides*, *Vibrio* spp, *Vibrio cholerae*, and *Yersinia enterocolitica*) and only reported in the medical record if the repeat test was positive. Positives for *Salmonella* spp., *Vibrio* spp., *Vibrio cholerae*, *Yersinia enterocolitica*, *Escherichia coli* O157, and *Shigella*/enteroinvasive *E. coli* (EIEC) were subsequently inoculated onto appropriate culture medium (see below) with additional selenite and Gram-negative broth (Becton, Dickinson and Co., Franklin Lakes, NJ [BD]) enrichment for *Salmonella* spp. and *Shigella* spp., respectively. Isolates grown from culture were sent to the Public Health Laboratory (PHL) at New York City Department of Health and Mental Hygiene. In the absence of culture growth, the GI panel result was still reported in the medical record and the original specimen was sent to the PHL. Original specimens from patients testing positive for *Cryptosporidium* spp, *Cyclospora cayetanensis*, and *Entamoeba histolytica* were sent to the Wadsworth Parasitology Laboratory at New York State Department of Health.

Conventional stool testing included stool culture with blood, MacConkey, Hektoen-enteric, cefsulodin-irgasan-novobiocin, *Campylobacter* selective, thiosulfate citrate bile salt, and sorbital MacConkey agars (BD). The stool ova and parasite exam included *Giardia* and *Cryptosporidium* spp. antigen testing (Meridian Biosciences, Inc., Cincinnati, OH), as well as modified acid-fast staining. Viral testing was performed for rotavirus and adenovirus 40/41 antigens by EIA (Premier Rotaclone and Adenoclone; Meridian Biosciences, Inc., Cincinnati, OH).

Outcomes and statistical analyses. Our primary outcome was clinical utilization following a stool test. We measured for associations between variables with stool test results via the chi-square test for categorical variables and the Student's *t* test for continuous variables. All tests were considered significant at a 2-sided *P* value less than 0.05. SPSS software (IBM) was used to perform all statistical analyses. The study was approved by the Columbia University Medical Center Institutional Review Board.

RESULTS

We identified 5,986 patients who underwent a conventional stool culture (3,379, 56.4%) or stool culture with ova and parasites exam (2,607, 43.6%) between December 2012 and February 2015, including 561 patients (9.4%) who were also tested for rotavirus and adenovirus by EIA. We then identified 9,402 patients who underwent GI panel testing between March 2015 and May 2017 (Table 1). Compared with patients who underwent a GI panel, patients who underwent conventional stool testing were more likely to be older (stool culture, median 45.5 years; GI panel, median 46.7 years; $P = 0.001$), tested during the winter (30.9% stool culture versus 24.4% GI panel, $P = 0.001$), and seen in outpatient settings (33.2% stool culture versus 30.3% GI panel, $P = 0.0011$).

Conventional stool testing was positive in 246 exams (4.1%) compared with 2,746 exams under PCR testing (29.2%, $P < 0.001$; Table S1). There were major differences in the distribution of pathogens detected between testing modalities (Table 2). Conventional stool testing was positive for 38 viruses (15.4%), 202 bacteria (82.1%), and 9 parasites (4.3%), with *Campylobacter* and *Salmonella* species as the most commonly identified pathogens. Only 5 patients (2.0%) had multiple pathogens detected. GI panel testing was positive for 1,073 viruses (39.1%), 1,792 bacteria (65.3%), and 226 parasites (8.2%), with enteropathogenic *Escherichia coli* (EPEC) and norovirus as the most commonly identified pathogens (Table 2). A total of 783 of the 2,746 positive patients (28.5%) had multiple pathogens detected.

Within 30 days following stool testing, compared with patients who received a conventional stool test, patients who received a GI panel were less likely to undergo endoscopic evaluation (GI panel, 787, 8.4%; stool culture, 576, 9.6%; $P = 0.008$; Table 3) or any abdominal radiology (GI panel, 2,760, 29.4%; stool culture, 1,897, 31.7%; $P = 0.002$). Within 14 days following stool testing, compared with patients who received a conventional stool test, patients who received a GI panel were less likely to be prescribed any antibiotic (GI panel, 3,408, 36.2%; stool culture, 2,449, 40.9%; $P < 0.001$). No differences were seen in length of stay or emergency department visits between the two groups.

These outcome metrics reflected the higher positivity rate of the GI panel than that of the conventional stool testing. For patients in both groups, the identification of one or more pathogens (a positive result) was associated with substantially lower utilization of endoscopy, abdominal radiology, and antibiotic prescribing compared with a negative result (Table S2).

DISCUSSION

In this retrospective study of 5,986 patients who underwent conventional stool testing from December 2012 to February 2015 and 9,402 patients who underwent a GI panel from March 2015 through May 2017, the implementation of multiplex PCR stool testing was associated with a significant reduction in the risk of receiving endoscopy, abdominal radiography, and antibiotics following a test. Overall, patients tested by PCR were 12.5% less likely to undergo endoscopy, 7.3% less likely to undergo abdominal imaging, and 11.4% less likely to be prescribed antibiotics than patients tested by conventional stool testing. The absolute risk was 1.1%, 2.3%, and 4.7% lower for endoscopy, abdominal radiology, and antibiotic prescriptions, respectively. Notably, the

TABLE 1 Demographics of study patients stratified by stool-testing modality

Demographic	GI PCR (n = 9,402)[a]	Stool culture and O&P[a,b] (n = 5,986)	P value
Sex			
Male	4,509 (48.0)	2,925 (48.9)	
Female	4,893 (52.0)	3,061 (51.1)	0.273
Test			
PCR	9,402 (100)	0	
Culture	0	379 (56.4)	
With rotavirus and adenovirus EIA		352/3,379 (10.4)	
Culture plus ova/parasites	0	2,607 (43.6)	
With rotavirus and adenovirus EIA		209/2,607 (8.0)	
Age at test (yrs)			
Median (IQR[c])	46.7 (19.6–65.9)	45.5 (15.4–64.4)	
Median (SD)	43.2 (27.0)	41.5 (27.7)	0.001
<18	2,236 (23.8)	1,625 (27.1)	
18–29	1,058 (11.3)	612 (10.2)	
30–49	1,730 (18.4)	1,046 (17.5)	
50–69	2,631 (28.0)	1,669 (27.9)	
>70	1,747 (18.6)	1,034 (17.3)	0.041
Yr of test			
March 2015–May 2017	9,402 (100)	0	
December 2012–February 2015	0	5,986 (100)	
Season			
Fall	2,104 (22.4)	1,396 (23.3)	
Spring	2,758 (29.3)	1,416 (23.7)	
Summer	2,249 (23.9)	1,326 (22.2)	
Winter	2,291 (24.4)	1,848 (30.9)	0.001
Region (by zip code)			
New York City	5,814 (61.8)	3,887 (64.9)	
Tri-state	3,396 (36.1)	1,163 (19.4)	
Other	192 (2.0)	936 (15.6)	0.001
Place of test			
Inpatient	5,514 (58.6)	3,361 (56.1)	
Outpatient	2,849 (30.3)	1,985 (33.2)	
Emergency department	1,036 (11.0)	640 (10.7)	0.001
Race			
Asian/Pacific Islander	320 (3.4)	178 (3.0)	
Black	951 (10.1)	682 (11.4)	
White	3,378 (35.9)	2,147 (35.9)	
Other/unknown	4,753 (50.6)	2,979 (49.8)	0.042
Ethnicity			
Hispanic	1,696 (18.0)	1,388 (23.2)	
Non-Hispanic	3,173 (33.7)	2,090 (34.9)	
Unknown	4,533 (48.2)	2,508 (41.9)	0.001
Inflammatory bowel disease	575 (6.1)	350 (5.8)	0.517
Celiac disease	488 (5.2)	287 (4.8)	0.290
HIV	313 (3.3)	309 (5.2)	0.001

[a]All values are number (percent) unless otherwise indicated.
[b]O&P, ova and parasite exam.
[c]IQR, interquartile range.

utilization of some procedures and imaging studies, such as colonoscopy and abdominal X ray, was actually higher in the PCR group, as some patients in that group underwent multiple procedures or imaging studies. Nevertheless, the overall risk to patients of receiving any endoscopic procedure or any abdominal imaging study was lower overall.

These utilization outcomes were likely driven by the increased sensitivity and higher

TABLE 2 Distribution of pathogens among positive results stratified by stool-testing modality

Patients and pathogens	GI PCR (n = 9,402)[a]	Stool culture, O&P, and rotavirus/adenovirus EIA (n = 5,986)[a]	P value
Patients with a pathogen	2,746/9,402 (29.2)	246/5,986 (4.1)	
Pathogens identified	3,804	251	
Viruses	1,073/2,746 (39.1)	38/246 (15.4)	0.001
Adenovirus F 40/41	89 (2.3)	5 (2.0)	0.298
Astrovirus	91 (2.4)		
Norovirus GI/GII	613 (16.1)		
Rotavirus A	176 (4.6)	35 (13.9)	0.001
Sapovirus (I, II, IV, and V)	158 (4.2)		
Bacteria	1,792/2,746 (65.3)	202/246 (82.1)	0.001
Aeromonas species		1 (0.4)	
Campylobacter species	309 (8.1)	110 (43.8)	0.001
Plesiomonas shigelloides	31 (0.8)	2 (0.8)	0.649
Salmonella species	147 (3.9)	56 (22.3)	0.001
Yersinia enterocolitica	75 (2.0)	0	0.009
Vibrio species	10 (0.3)	0	0.343
Vibrio cholerae	5 (0.1)	0	0.899
Escherichia coli subtypes	1,420/2,746 (51.7)	4/246 (1.6)	0.001
Enteroaggregative *E. coli*	530 (13.9)		
Enteropathogenic *E. coli*	863 (22.7)		
Enterotoxigenic *E.coli* (LT/ST)	167 (4.4)		
Shiga-like toxin-producing *E.coli* STX/ST2	131 (3.4)		
E. coli 0157	21 (0.6)	3 (1.2)	0.444
Shigella/enteroinvasive *E. coli*	156 (4.1)	29 (11.6)	0.001
Parasite	226/2,746 (8.2)	9/246 (3.7)	0.011
Cryptosporidium sp.	92 (2.4)	5 (2.0)	0.264
Cyclospora cayetanensis	13 (0.3)	0	0.279
Entamoeba histolytica	2 (0.1)	2 (0.8)	0.002
Giardia lamblia	125 (3.3)	2 (0.8)	0.005
Multiple pathogens	783/2,746 (28.5)	5/246 (2.0)	0.001

[a]All values are number (percent).

positivity rate of the GI panel, as patients were less likely to undergo additional interventions if they tested positive by either method. The GI panel testing was positive in 29.2% of cases compared with only 4.1% positivity of conventional stool tests. Health care providers may feel assured that a positive stool test provides a definitive diagnosis, making it less likely that they will order additional studies (endoscopy and abdominal radiology). Similar data were found by Beal et al. in a study of 241 GI panels compared with historical controls, where patients tested on the GI panel had fewer other infectious stool tests, numbers of days on antibiotics, abdominal and/or pelvic imaging studies, and LOS with an overall estimated reduction in health care costs (14).

To our knowledge, our study is the largest to date examining resource utilization following multiplex PCR stool testing compared with previous, conventional testing. While the identification of a pathogen by any method resulted in decreased downstream resource utilization compared with negative testing, this effect was especially notable for antibiotic prescribing following a GI panel. This may be due to the increased ability to detect viral gastroenteritis by PCR technology. As such, a significant proportion of patients were able to avoid antibiotic exposure and its attendant risks altogether, illustrating the use of novel diagnostics in facilitating antibiotic stewardship. A prospective, multicenter study of the GI panel similarly showed that patients diagnosed by PCR were less likely to receive empirical antimicrobials (15).

Our positivity rate was lower than other reports in the literature on multiplex PCR stool testing, ranging from 30% to more than 70%.(4, 12, 13, 16, 17) Previously, we reported data from our institution demonstrating a 35% positivity rate in outpatients and a lower positivity rate for patients with underlying diarrheal diseases, such as inflammatory bowel disease and celiac disease.(5, 7, 10, 18) We found similar propor-

TABLE 3 Patient outcomes and resource utilization stratified by stool-testing modality

Variable	GI PCR (n = 9,402)[a]	Culture (n = 5,986)[a]	P value
Endoscopy within 30 days			
No procedures	8,615 (91.6)	5,410 (90.4)	0.008
Any procedure	787 (8.4)	576 (9.6)	0.008
Upper endoscopy	480 (5.1)	302 (5.0)	0.862
Sigmoidoscopy	71 (0.8)	46 (0.8)	0.920
Enteroscopy	10 (0.1)	7 (0.1)	0.841
Colonoscopy	453 (4.8)	223 (3.7)	0.007
Emergency department visit within 30 days	1,158 (12.3)	789 (13.2)	0.116
Radiology within 30 days			
Any abdominal radiology	2,760 (29.4)	1,897 (31.7)	0.002
Abdominal X ray	1,364 (14.5)	861 (14.4)	0.831
Barium enema	20 (0.2)	12 (0.2)	0.871
CT abdomen/pelvis	1,195 (12.7)	796 (13.4)	0.290
CT enterography	10 (0.1)	8 (0.1)	0.629
Esophagram	83 (0.9)	19 (0.3)	0.001
HIDA	22 (0.2)	24 (0.4)	0.064
MR abdomen/pelvis	275 (2.9)	156 (2.6)	0.243
MR enterography	58 (0.6%)	38 (0.6)	0.890
Upper GI series	67 (0.7)	362 (6.0)	0.001
Ultrasound abdomen	1,103 (11.7)	753 (12.6)	0.115
Nonabdominal radiology			0.001
CT chest	953 (10.1)	557 (9.3)	0.091
Chest X ray	2,908 (30.9)	2,042 (34.1)	0.001
Any radiology	4,521 (48.1)	2,759 (46.1)	
Antibiotics within 14 days			
Any antibiotic	3,408 (36.2)	2,449 (40.9)	0.001
Metronidazole	235 (2.5)	3 (0.1)	0.001
Penicillin	1,366 (14.5)	1,158 (19.3)	0.001
Cephalosporin	1,259 (13.4)	939(15.7)	0.001
Carbapenem	519 (5.5)	370 (6.2)	0.086
Aminoglycoside	516 (5.5)	483 (8.1)	0.001
Quinolone	804 (8.6)	612 (10.2)	0.001
Macrolide	456 (4.9)	390 (6.5)	0.001
Tetracycline	50 (0.5)	81 (1.4)	0.001
Length of stay from test to discharge			
Median (IQR)	5 (2–13)	5 (2–13)	
Mean (SD)	12.4 (21.9)	11.8 (20.0)	0.087

[a]All values are number (percent) unless otherwise indicated.

tions of bacterial, viral, and parasitic pathogens compared with previous data in the literature and, similarly, found a greater proportion of infections in younger patients, particularly viruses. Given our large sample size and censorship of patients with *C. difficile*, these results may more accurately reflect true clinical practice. It is also possible that the lower positivity rate is due to our broad inclusion criteria or, more likely, the increasing inappropriate utilization of the test, as the high number of inpatient tests suggests it may not have always been ordered for episodes of acute gastroenteritis. This may also explain the failure to identify a reduced length of stay under GI panel testing.

There are several limitations to the current study inherent to a retrospective design. Our analyses do not prove a cause and effect relationship between diarrhea, the identification of specific enteric infections, and patient outcomes. Individual patient information concerning precise presenting symptoms, medication exposures, recent travel, sexual behavior, other comorbid conditions, and precise management, including antibiotic duration after stool testing, was not available for full analysis. PCR testing may also fail to discriminate between active infection, asymptomatic colonization, and detection of nonviable nucleic acids. In addition, thresholds for testing in specific patient populations may influence the overall rate of detection, as seen, for example,

among patients at our center with inflammatory bowel disease (IBD) who undergo frequent panel testing but are less likely to test positive than patients without IBD (5, 7, 18); however, we do not believe this would significantly influence the distribution of particular infections detected. Although the patient population was ethnically and geographically diverse, the majority of patients resided in the Northeast United States. Moreover, although we reviewed consecutive testing periods between 2012 and 2017, we cannot fully account for changes in ordering patterns over time, and patients from the two groups were tested during two separate time frames. Although differences were seen in some baseline demographics between the GI panel and the conventional testing groups, it is important to note that these differences actually favored the conventional testing group, who were younger and more likely to be outpatients and, thus, required fewer interventions, such as radiography, endoscopy, and antibiotics. Thus, the true effect size with the GI panel was diminished by these baseline differences.

Despite these limitations, in this large analysis of patients who underwent stool testing, multiplex PCR was associated with modest but significant reductions in endoscopy, abdominal radiography, and antibiotic prescribing compared with conventional testing. Coupled with high sensitivity and rapid turnaround, multiplex PCR stool testing has the potential to optimize health care utilization and reduce costs, although the cost-effectiveness of multiplex assays for acute gastroenteritis has not been fully determined (12). As the availability of multiplex PCR stool testing continues to increase, additional studies are needed to evaluate how the results of these assays inform clinical management decisions and what the overall impact is on patient and health care outcomes.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/JCM.01775-18.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

SUPPLEMENTAL FILE 2, PDF file, 0.1 MB.

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