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Comparison of Multiplex Gastrointestinal Pathogen Panel and Conventional Stool Testing for Evaluation of Diarrhea in Patients with Inflammatory Bowel Diseases

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Abstract

Background and Aims: Gastrointestinal pathogen panels (GPP) are increasingly being used for evaluation of diarrhea. The impact of these tests in patients with inflammatory bowel diseases (IBD) is unknown. We performed a time-interrupted cohort study comparing GPPs and conventional stool evaluation in patients with IBD with diarrhea.

Methods: We included 268 consecutive patients with IBD who underwent GPP (Biofire Diagnostics®) (n=134) or conventional stool culture and Clostridium difficile polymerase chain reaction (PCR) testing (n=134) during suspected IBD flare between 2012–2016. Primary outcome was composite of 30-day IBD-related hospitalization, surgery or emergency department visit; secondary outcome was IBD treatment modification.

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- Study concept and design: WA, WJS, SS
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ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This study was approved by the UCSD Institutional Review Board (IRB #161914)

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Results: Overall, 41/134 (30.6%) patients tested positive on GPP (18 C.difficile, 17 other bacterial infections, 6 viral pathogens) vs. 14/134 patients (10.4%, all C.difficile) testing positive on conventional testing. Rate of IBD treatment modification in response to stool testing was lower in GPP group as compared conventional stool testing group (35.1% vs. 64.2%, p<0.01). On multivariate analysis, diagnostic evaluation with GPP was associated with 3-times higher odds of IBD-related hospitalization/surgery/ED visit (95% CI, 1.27–7.14), as compared to conventional stool testing. This negative impact was partly mediated by differences in ordering provider specialty, with non-gastroenterologists more likely to order GPP as compared to gastroenterologists.

Conclusions: In patients with suspected flare of IBD, GPPs have higher pathogen detection rate and lead to lower rate of IBD treatment modification. A diagnostic testing strategy based on GPPs is associated with higher hospital-related healthcare utilization as compared to conventional stool testing, particularly when utilized by non-gastroenterologists.

Keywords

Diagnostic testing; nucleic acid detection; over-diagnosis; complications

INTRODUCTION

Gastrointestinal infections present an important conundrum in the management of inflammatory bowel disease (IBD). Gastrointestinal infections, in particular *Clostridium difficile* (CDI), are common in patients with IBD.[1] In patients with known IBD, a flare of IBD may be indistinguishable from acute infectious gastroenteritis with patients presenting with diarrhea, rectal bleeding and abdominal pain; moreover, gastrointestinal infections as well as antibiotic use may themselves trigger a flare of IBD.[2] Hence, stool testing for gastrointestinal infection is an essential first step in the evaluation of an IBD patient presenting with symptoms of a flare. Conventionally, stool testing has been performed using stool cultures for bacterial pathogens and *Clostridium difficile* toxin testing using polymerase chain reaction (PCR).

Over the last 5 years, the United States Food and Drug Administration has approved multiplex gastrointestinal pathogen panels (GPPs) for evaluation of patients suspected to have acute infectious gastroenteritis.[3] These tests simultaneously evaluate for a large number of bacterial, viral and/or parasitic pathogens by detection of microbial nucleic acids. Compared to conventional stool tests, GPP offer several advantages such as reduced technical expertise, shorter turnaround times, consolidated workflow, and increased sensitivity.[3, 4] However, GPP is highly sensitive and cannot distinguish between viable, replicating organisms that are responsible for disease and nonviable pathogens or remnant nucleic acid (colonization); several ‘pathogens’ on this panel such as E.coli species (enteropathogenic *E.coli* [EPEC] or enteroaggregative *E.coli* [EAEC]), adenovirus, astrovirus, *Salmonella,* etc. may be present in the stool of asymptomatic individuals, or may be shed for long periods of time after resolution of disease.[5] This may be problematic in patients who have underlying chronic gastrointestinal diseases such as IBD, wherein positive results may be truly pathogenic or may represent over-diagnosis with misattribution of symptoms to infections, inappropriate use of antibiotics, and delay in IBD-directed therapy.

There has been very limited comparative evaluation of clinically relevant outcomes in patients with IBD who undergo GPP as compared to conventional stool testing. In a study from Mayo Clinic, based on conventional stool examination, non-CDI bacterial infections were very uncommon (<3%) in patients with IBD, and were largely inconsequential.[6] In contrast, in another referral center study, ~14% patients with IBD who underwent GPP were positive for non-CDI infections, of which 1/3rd were treated with antibiotics; these patients were less likely to undergo IBD treatment modification as compared to patients who tested negative. However, this study did not evaluate downstream patient-important consequences of testing and associated treatment decisions.[7] Hence, we conducted a retrospective cohort comparing risk of clinically relevant outcomes (30- and 90-day risk of surgery, hospitalization and/or emergency department [ED] visits) in biologic-exposed patients with IBD who underwent conventional stool testing (stool culture for bacterial pathogens and *C.difficile* toxin PCR testing) or multiplex GPP for evaluation of suspected IBD flare. Our study was designed to evaluate the impact of diagnostic approach, rather than focusing on results of specific tests, on outcomes of patients.[8]

METHODS

Study Design:

We performed a retrospective cohort study in biologic-exposed patients with IBD seen and followed at University of California San Diego (UCSD). Patients were included if they had a definitive diagnosis of IBD (based on clinical history, endoscopy, radiology and/or histology), were treated with biologic agents any time between January 1, 2012 to December 31, 2016, were followed at UCSD for >6 months, and underwent stool testing for suspected symptoms of IBD flare (diarrhea, rectal bleeding, and/or abdominal pain). This study was approved by the UCSD Institutional Review Board (IRB #161914).

Enteric Pathogen Testing:

Between 2012 to 2015, infectious evaluation for diarrhea was performed exclusively using conventional stool testing (stool culture and *C difficile* PCR). *C. difficile* PCR test at our institution detects *C. difficile* toxin B gene (tcdB), and is an FDA-cleared in-vitro diagnostic test that has been modified with performance characteristics validated by the UC San Diego Health System Clinical Laboratories. In September 2015, our institution started using GPP, BioFire FilmArray GI Panel® (BioFire Diagnostics, Salt Lake City, UT), for both inpatient and outpatient diarrhea evaluation.[4] This test detects nucleic acid from 22 pathogens including 13 bacteria, 5 viruses, and 4 parasites, including *C. difficile* genes for both toxins A (tcdA) and B (tcdB). The GPP is practically used by providers in the outpatient setting, emergency department, and early inpatient setting; it cannot be ordered at our institution for inpatients that have been hospitalized greater than 72 hours, as by that point, any diarrheal diagnostic testing is focused on *C. difficile* detection. Processing (hands-on) time per run takes approximately two minutes, there is no separate extraction required, results return in approximately one hour, and report dichotomous results (detected or not detected).[3] Between January 1 to November 30, 2016, at UCSD, we performed 862 stool cultures tests and 2145 GPPs, in both inpatient and outpatient setting in all patients. Approximately 4.2% stool cultures tested positive, and ~10% *C.difficile* PCR tests were positive. Of all GPP tests

performed, overall positivity is 36% (including *C.difficile* 15.3%, EPEC 9.5%, EAEC 4.9%, norovirus 5.1%, Shigella/Enteroinvasive E.coli 3.4% and Campylobacter 2.4%).

Patients who underwent either form of testing during an episode suggestive of a flare were included; patents who underwent repeated stool evaluation over the course of their follow-up at UCSD, only a single test was included. To avoid differential testing bias based on provider preferences, we performed a time-interrupted cohort study in which all patients included in the conventional testing arm underwent testing between 2012–15 (when that was the only evaluation available), and all patients included in the GPP testing arm had undergone evaluation between 2015–16. While providers from 2015–16 could choose to order conventional testing, GPP, or both, providers often chose only one of the two diagnostic evaluation methods. Since the outcomes were defined at a fixed 30- and 90-day follow-up, differential length of follow-up in these cohorts was inconsequential.

Data Abstraction:

We abstracted the following values from the medical records: (a) patient characteristics: age, sex, race or ethnicity, body mass index; (b) disease characteristics: IBD type, phenotype (based on Montreal classification), disease duration, disease location, prior bowel resection, hospitalization within 6 months prior to presentation, CDI and/or antibiotic use within 12 months prior to presentation; (c) treatment characteristics: current biologic and/or immunomodulator use, prior biologic use, current steroid use or use within 12 months prior to presentation; (d) flare characteristics: symptoms at presentation (diarrhea, blood in stool, fever, abdominal pain), laboratory variables at presentation (white blood cell count, hemoglobin, C- reactive protein, albumin); (e) enteric pathogen testing: test type, identified pathogen(s), ordering providers (gastroenterologists vs. non-gastroenterologists); and (f) outcomes: composite of IBD-related surgery, hospitalization and/or ED visit within 30 days or 90 days of enteric pathogen testing, IBD treatment modification (change in corticosteroids, immunomodulators and/or biologic) or initiation of antibiotics following enteric pathogen testing.

Outcomes:

Primary outcome of interest was rate of IBD-related surgery, hospitalization and/or ED visit within 30 days of enteric pathogen testing, regardless of test results. Secondary outcomes were: (a) IBD-related surgery, hospitalization and/or ED visit within 90 days of enteric pathogen testing, (b) IBD treatment modification in response to enteric pathogen testing (change in corticosteroids, immunomodulators and/or biologic use), and (c) initiation of antibiotics in response to enteric pathogen testing.

We also compared outcomes in patients who tested positive vs. negative on corresponding enteric pathogen testing modality. Subgroup analysis of patients with ulcerative colitis or Crohn’s disease was also performed.

Statistical Analysis:

We evaluated the association between type of enteric pathogen testing and outcomes and covariates using Chi-square test or Fisher’s Exact test for categorical variables and Student’s

t-test for continuous variables. To evaluate the independent association between type of enteric pathogen testing and clinical outcomes, we performed multivariable logistic regression analysis after adjusting for age, prior hospitalization, current biologic and/or steroid use and C-reactive protein. All hypothesis testing was performed using a two-sided p-value with a statistical significance threshold <0.05. All statistical analyses were performed with Stata MP (StataCorp. 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP).

RESULTS

Patient Characteristics

We included 268 symptomatic IBD patients (42.5% with ulcerative colitis; 57.5% with Crohn's disease) who underwent stool testing (50% conventional stool testing; 50% GPP) during the study period. Baseline patient, disease, treatment and clinical presentation characteristics are summarized (Table 1). Majority of patients presented with diarrhea and/or abdominal pain; 27.6% presented with rectal bleeding, and 7.8% patients had fever at presentation. Overall, 6.7% patients had prior CDI in preceding 12 months. Patients undergoing GPP had longer disease duration (median, 9 years vs. 6 years, p<0.01), higher rate of prior bowel resection (43% vs. 26%, p<0.01) and prior anti-TNF exposure (99% vs. 69%, p<0.01), and were more likely to be on biologics at time of enteric pathogen testing (76% vs. 51%, p<0.01). However, these patients who underwent GPP testing were less likely to have been hospitalized in the preceding 6 months (16% vs. 35%, p<0.01), received corticosteroid use within 12 months prior (30% vs. 46%, p=0.01), though there was no difference in current corticosteroid use (19% vs. 24%, p=0.46). Gastroenterologists were more likely to order conventional stool testing over GPP (61% vs. 39%), whereas non-gastroenterologists were more likely to order GPP testing over conventional stool testing (62% vs. 38%).

Enteric Pathogen Testing

Overall, 41/134 (30.6%) patients tested positive using GPPs, with 51 total organisms identified. The most common enteric pathogens detected by GPP were *E. coli* species (19, 14.2%; mainly enteropathogenic *E.coli* [EPEC] or enteroaggregative *E.coli* [EAEC]) and CDI (18, 13.4%). Other pathogens detected included Campylobacter, Salmonella, Yersinia, Plesiomonas, Shigella, Norovirus, Rotavirus, and Adenovirus (Table 2). Eight (6.0%) patients were noted to have co-infections, with two or more detected pathogens. Overall, these GPP positivity rates were comparable to rates observed institution-wide regardless of underlying disease (36%). Patients undergoing GPP did not undergo concomitant conventional stool testing. In contrast, 14/134 (10.4%) patients undergoing conventional stool testing had positive tests with 14 total organisms identified, all of which were CDI; no cases of non-CDI bacterial pathogens were identified on conventional stool culture. This was also comparable to overall institution-wide *C.difficle* PCR positivity (10%) and stool culture positivity (4.2%).

Impact of Enteric Pathogen Testing on Clinical Outcomes

Primary Outcome: Overall, 24 (18%) patients underwent GPP testing underwent IBD-related surgery, hospitalization and/or ED visit within 30 days of testing, as compared to 20 (15%) patients who underwent conventional stool testing (Table 3). Similar results were obtained when evaluating 90-day rates of IBD-related surgery, hospitalization and/or ED visit (Table 3), and in patients with ulcerative colitis and Crohn's disease (eTable 1 and 2). On multivariable logistic regression, after adjusting for age, prior hospitalization, current biologic and/or steroid use and C-reactive protein, diagnostic evaluation with GPP was associated with 3 times higher odds of IBD-related hospitalization/surgery/ED visit within 30 days of testing (OR, 3.03; 95% CI, 1.27–7.14), as compared to conventional stool testing (Table 4). Besides enteric pathogen testing modality, current corticosteroid use and high C-reactive protein were associated with increased risk of outcomes, whereas current biologic use was protective against hospitalization-related healthcare utilization.

To assess whether impact of GPP testing on outcomes may be influenced by ordering provider, we added ordering provider to the multivariable model (Table 4). Non-gastroenterologist as ordering provider was independently associated with higher odds of IBD-related hospitalization/surgery/ED visit within 30 days of testing (OR, 3.73; 95% CI, 1.34–10.36), whereas the independent impact of GPP testing was not significant.

Secondary outcomes:

IBD treatment modification: Patients who underwent GPP testing were significantly less likely to undergo IBD treatment modification in response enteric pathogen testing as compared to patients who underwent conventional stool testing (35% vs. 64%, $p<0.01$). Patients undergoing GPP testing were less likely to have addition of corticosteroids, change in biologics as well as immunomodulator use (Table 3). These results were stable in subgroup analyses in patients with ulcerative colitis or Crohn's disease (eTable 1 and 2).

Antibiotic use: Thirty-five (26.1%) patients who underwent GPP received antibiotics compared to 26 (19.4%) patients undergoing conventional stool testing ($p=0.24$). Among GPP-positive patients, 15 (42.9%) received antibiotics for CDI, 12 (34.3%) received antibiotics for non-CDI bacteria, and 8 (22.9%) patients received antibiotics for alternative indications (suspected pouchitis, perianal fistula, suspected intra-abdominal abscess and/or suspected gastrointestinal infection); 3 patients detected to have CDI on GPP testing did not receive antibiotics. Among patients who were positive on conventional stool testing, 14 (53.8%) patients received treatment for CDI and 12 (46.2%) received antibiotics for alternative indications.

Enteric pathogen test positivity vs. negativity: There was no significant difference in 30- or 90-day rates of IBD-related surgery, hospitalization and/or ED visit between patients who tested positive or negative on GPP, and in patients who tested positive or negative on conventional stool testing (eTable 3). Numerically, rate of addition of corticosteroids was lower in patients who tested positive vs. negative on GPP testing (24% vs. 12%, $p=0.13$). On multivariate logistic regression among a subset of patients who

underwent GPP testing, test positivity vs. negativity did not significantly affect risk of 30-day hospitalization-related healthcare utilization (data not shown).

DISCUSSION

In this time-interrupted, retrospective cohort study of 268 patients with IBD, who underwent either conventional stool testing using stool culture and *C.difficile* toxin PCR testing or multiplex GPP for symptoms suggestive of IBD flare, we made several key observations. First, enteric pathogen positivity was almost 3 times higher with GPP testing than conventional stool testing in patients with IBD; this rate aligns with overall GPP test positivity at our center across all patient populations. Overall rates of CDI detection were comparable between both tests, but GPP identified 19 additional patients as having non-CDI bacterial infections, primarily *E.coli* species (EPEC and EAEC) and 4 patients with viral pathogens; conventional stool cultures were negative for non-CDI bacteria. Second, after adjusting for important covariates, patients who underwent GPP testing had 3-times higher odds of having IBD-related surgery, hospitalization or ED visit within 30 days of testing, as compared to patients who underwent conventional stool testing. This effect was partly mediated by ordering providers. Patients who underwent stool testing by non-gastroenterologists vs. gastroenterologists experienced higher rates of adverse outcomes. This may be related to challenges in test interpretation and action by non-gastroenterologists, rather than actual test findings. This is apparent based on our observation that patients undergoing GPP testing were more likely to receive antibiotics, and less likely to have their IBD- related medications changed, as compared to patients who underwent conventional stool testing.

By specifically focusing on impact of a diagnostic approach (GPP vs. conventional stool testing), rather than focusing on test results, on patient-important outcomes, we are able to directly inform clinical practice. Our findings suggest that GPP testing to rule out infections in IBD patients presenting with symptoms suggestive of flare is associated with adverse patient outcomes with higher rates of hospitalization- related healthcare utilization. We hypothesize that higher enteric infection positivity on GPP testing leads to misattribution of IBD symptoms to infections especially by non-gastroenterologists, and consequent delay in IBD-related treated modification and/or excessive use of antibiotics resulting in higher rates of ED visit, hospitalization and/or surgery. Based on these findings, GPP testing in patients with IBD, especially when applied by non-gastroenterologists, likely represents low-value care with potential for harm. As such, limiting diagnostic testing to *C. difficile* evaluation may be most appropriate at this time due to its clinical significance within this population.

GPPs were approved by the FDA for rapid and simultaneous detection of multiple gastrointestinal pathogens simultaneously in patients with signs and symptoms suggestive of gastrointestinal infections.[4, 5] While several cross-sectional studies have confirmed higher sensitivity of these tests, there has been very limited evaluation of downstream consequences of GPP testing on clinically relevant outcomes. Concerns regarding misattribution of symptoms or misdiagnosis of infection in patients with asymptomatic colonization, as well as healthcare provider confusion of interpretation of test results (such as EPEC or EAEC positivity, detection of multiple pathogens) with broad implementation of these tests have

been raised.[3, 4] In hospitalized patients, inappropriately treating GPP-positive asymptomatic patients with colonization can lead to unnecessary patient isolation, longer length of stay, poor antibiotic stewardship, and institutional penalties for artificially high infectious diarrhea rates. Similar to IBD, over-reliance on GPP testing may potentially delay diagnosis and treatment of other non- infectious diarrhea, that may be seen in other immunocompromised patients (for example, post chemotherapy), organ transplant recipients, patients with human immunodeficiency virus, etc.

Patients with IBD represent a unique population when using GPPs based on the overlap in symptoms between gastrointestinal infections and IBD flare, dysbiosis with higher baseline prevalence of specific and potentially pathogenic *E.coli* species, such as adherent-invasive *E.coli* in patients with IBD, as well as potential for IBD flare due to potentially pathogenic bacteria or subsequent antibiotic exposure.[2, 9] There has been limited evaluation of GPPs in patients with IBD. In a single-center study, Axelrad and colleagues evaluated outcomes in 214 symptomatic patients with IBD who underwent 295 GPP using BioFire Film Array and *C.difficile* PCR testing.[7] In their cohort, 12.9% tested positive for CDI, and 13.9% tested positive on the GPP for other non-CDI pathogens (primarily *E.coli* species), comparable to our cohort. Approximately 50% patients who tested positive for non-CDI bacterial pathogens were treated with antibiotics, as compared to 34.3% in our cohort. Comparing patients with positive test results on GPP for non-CDI pathogens and negative tests, they did not observe any significant differences in rates of hospitalization or surgery, though rate of IBD treatment modification was higher in those with negative results. In another single-center study of 131 patients with IBD (89% inpatients, 47% on biologics, 88% with objective evidence of active IBD) published only in abstract form, Limsrivilai and colleagues, ~30% tested positive for enteric pathogens on GPP. GPP positivity was significantly higher in patients with active IBD-related inflammation (33% vs. 6% in patients without active IBD).[10] They observed lower rates of escalation of IBD-related therapy and surgery in the short-term in those who tested positive on GPP, as compared to those who tested negative, interpreting that short-term course of IBD may be more benign in those who test positive on GPP as compared to those who test negative. However, it is unclear whether this represents in-hospital outcomes or longer-term outcomes, and whether this may be due to a diagnostic dilemma that treating clinicians faced, resulting in potential delay in IBD-treatment modification in this retrospective study. In contrast, in a recent study from Mayo Clinic using conventional stool testing in IBD patients presenting with flare, rate of non-CDI bacterial infections was very low (<3%), and did not influence disease course over 1 year, as compared to IBD patients who tested negative for infection or in patients with CDI; similar to this study, conventional stool testing in our study did not identify a single non-CDI pathogen.[6] Furthermore, a recent study from Columbia University Medical Center using GPP testing in IBD patients presenting with flare showed that GPP-positive patients treated with antibiotics for non-CDI had no difference in outcomes at median follow-up 10.5 months compared to untreated GPP- positive patients for non-CDI.[12] While further studies assessing outcomes for non-CDI in IBD patients are needed, currently a *C. difficile* toxin PCR only diagnostic strategy and/or increasing scrutiny prior to prescribing antibiotics for a positive GPP test is warranted. To our knowledge, ours is the first study that directly compares patient outcomes in patients who underwent GPP testing vs. those who underwent

conventional stool testing. GPP testing, regardless of test results, was associated with higher hospitalization-related healthcare utilization, along with lower rates of IBD- treatment modification.

Our study has several limitations, intrinsic to its retrospective design. First, a causal association between GPP testing and adverse patient outcomes cannot be established. This observation is likely multifactorial, with final decisions on IBD management and stool testing interpretation made based on case-by-case basis by treating physicians, with little evidence-based guidance. We were unable to explicitly test our hypothesis that delay in modification of IBD-related therapies directly contributed to increased healthcare utilization. Second, we designed our study to evaluate the impact of diagnostic approach, rather than focusing on results of specific tests, on outcomes of patients, as is recommended in evaluating quality of evidence supporting diagnostic tests.[8] Our study was not powered to detect differences in outcomes in patients with positive or negative results on GPP testing; rather, ours was a convenience sample of biologic-exposed patients with IBD seen and followed at a tertiary center over a 5-year period over which we transitioned from conventional stool testing to GPP. To maintain independence of individual subjects, we counted each patient only once, though most patients expectedly underwent multiple stool tests. Third, simultaneous GPP and CDI testing for toxin were not performed. While there has been no study to assess diagnostic performance of GPP against ‘gold standard’ (i.e. stool culture for bacterial pathogens, etc.) among IBD patients, not performing concomitant stool testing with GPP and conventional methods prevents the ability to accurately determine whether positivity on GPP was indicative of active infection. Fourth, our study population included a mix of outpatients and inpatients, seen in multiple different settings such as a primary care clinic, gastroenterology clinic, a specialized IBD clinic, ED or inpatient hospitalization with threshold and experience for testing likely different between providers in each setting. Fifth, providers could choose to order conventional testing, GPP, or both as diagnostic testing was not randomized from 2015–16. As such, selection bias could have occurred if certain providers preferentially opted for one testing method. However, there is low suspicion for significant differences in patient or disease characteristics for IBD patients undergoing either test in this time period.

In conclusion, based on a comparative retrospective cohort study in biologic- exposed patients with IBD presenting with symptoms suggestive of IBD flare, GPP testing is associated with increased risk for 30-day IBD-related ED visit, hospitalization, or surgery, higher rate of antibiotic prescription and lower rate of IBD-related treatment modification. GPP tests were more likely to be performed by non-gastroenterologists suggesting that interpretation and downstream actions by non-gastroenterologists may contribute to adverse outcomes seen in these patients. We recommend that positive test results on GPPs should be interpreted cautiously, with confirmation of non-CDI bacterial pathogens with stool culture where possible, before attributing symptoms to infection, rather than underlying IBD. This should not delay potential modification of IBD-directed therapy, which would be required in a majority of patients. Additionally, due to low rate of non-CDI bacterial culture positivity, conventional stool testing in IBD patients may be limited to *C.difficile* toxin PCR. Prospective studies directly evaluating the impact of GPP testing in patients with IBD are warranted, with assessment of etiologic predictive value of tests.[11]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of patients with inflammatory bowel diseases who underwent enteric pathogen testing using either conventional stool evaluation or multiplex gastrointestinal pathogen panels

	Conventional stool evaluation (N=134)	Gastrointestinal Pathogen Panel (N=134)	p-value
Patient Characteristics			
Age (years), mean +/− SD	38.9 ± 16.1	41.7 ± 16.1	0.16
Female, n (% total)	74 (55%)	68 (51%)	0.54
Race/ethnicity, n (%)			
• White	105 (78%)	97 (72%)	**0.03**
• Black	5 (4%)	5 (4%)	
• Hispanic	15 (11%)	15 (11%)	
• Asian	6 (4%)	2 (1%)	
• Other	3 (2%)	15 (11%)	
BMI (kg/m^2), mean +/− SD	24.3 ± 4.9	25.4 ± 6.5	0.13
Disease Characteristics			
Duration, (years), median (range)	6 (2–13)	9 (5–19)	**<0.01**
IBD Subtype, n (%)			
Crohn's disease	79 (59%)	75 (56%)	0.71
Ulcerative Colitis	55 (41%)	59 (44%)	
CD location, n (%)			
L1	10 (12%)	16 (21%)	0.16
L2	27 (34%)	18 (24%)	
L3	42 (53%)	39 (52%)	
L4	0 (0%)	2 (3%)	
UC Location, n (%)			
Pancolitis	28 (51%)	35 (60%)	0.62
Left-sided	17 (31%)	16 (27%)	
Proctitis	10 (18%)	8 (13%)	
Prior abdominal surgery, n (%)	35 (26%)	57 (43%)	**<0.01**
• Last 6 m	10 (7.5%)	9 (7%)	1.0
Prior hospitalization (last 6m), n (%)	47 (35%)	22 (16%)	**<0.01**
Prior antibiotic use (last 12m), n (%)	37 (28%)	30 (22%)	0.40
Prior CDI (last 12m), n (%)	14 (10%)	4 (3%)	**0.03**
Treatment Characteristics			
Prior anti-TNF exposure, n (%)	93 (69%)	133 (99%)	**<0.01**

	Conventional stool evaluation (N=134)	Gastrointestinal Pathogen Panel (N=134)	p-value
Prior steroid use (last 12m), n (%)	61 (46%)	40 (30%)	**0.01**
Current medication use			
• Immunomodulator use, n (%)	78 (58%)	59 (44%)	**0.04**
• Steroid use, n (%)	32 (24%)	25 (19%)	0.46
• Biologic use, n (%)	68 (51%)	102 (76%)	**<0.01**
Clinical Presentation			
Symptoms at presentation, n (%)			
• Diarrhea	115 (86%)	100 (75%)	**0.03**
• Blood in stool	38 (28%)	36 (27%)	0.89
• Fever	11 (8%)	10 (7%)	1.0
• Abdominal Pain	81 (60%)	95 (71%)	0.09
Labs at presentation			
• WBC (1000/mm^3), median (range)	8.1 (6.5 – 10.8)	8.2 (6.7 – 11.1)	0.59
• Hemoglobin (gm/dL), median (range)	12.8 (11.6 – 13.8)	13.2. (11.4 – 14.5)	0.41
• C-reactive protein (mg/dL), median (range)	0.8 (0.2 – 3.8)	1.0 (0.2 – 3.1)	0.77
• Albumin (g/dL), median (range)	4.1 (3.7 – 4.5)	3.9 (3.7 – 4.4)	0.28
Ordering provider			
• Gastroenterologists	88 (66%)	57 (43%)	0.01
• Non-gastroenterologists	46 (34%)	77 (57%)	
◦ Emergency department	6	25	
◦ Inpatient hospitalization	39	51	
◦ Medicine clinic	1	1	

[Abbreviations: BMI=Body mass index; CD=Crohn's disease; CDI=Clostridium difficile infection; IBD=Inflammatory Bowel Diseases; TNF=Tumor necrosis factor; UC=Ulcerative colitis; WBC=White blood cell]

Table 2.

Identification of enteric pathogens in patients with IBD, detected using conventional stool testing or gastrointestinal pathogen panels.

	Conventional stool evaluation (N=134)	Gastrointestinal Pathogen Panel (N=134)
Positive test, n (%)	14/134 (10%)	41/134 (31%)
Total # organisms Identified	14	51
Bacteria, n	**14**	**42**
CDI	14/14	18/51
Non-CDI Bacteria	0/14	24/51
• Escherichia coli species	0	19
◦ EAEC		6
◦ EPEC		11
◦ ETEC		2
• Campylobacter	0	1
• Salmonella	0	1
• Yersinia	0	1
• Plesiomonas	0	1
• Shigella	0	1
Viral, n	**0/14**	**9/51**
• Norovirus		6
• Rotavirus		2
• Adenovirus		1
Parasites, n	**0**	**0**
Co-infections, n	**0**	**8**
Treated with antibiotics, n	**26**	**35**
CDI	14	15
Non-CDI Bacteria	0	12
Alternative indication	12	8

[Abbreviations: CDI=Clostridium difficile infection; EAEC=Enteroaggregative E.coli; EPEC=Enteropathogenic E.coli; ETEC=Enterotoxigenic E.coli]

Table 3.

Association between enteric pathogen testing and 30- and 90-d risk of hospitalization- related health care utilization and change in IBD management

	Conventional stool evaluation (N=134)	Gastrointestinal Pathogen Panel (N=134)	p-value
Primary Outcome (30-day)			
Hospitalization-related health care utilization (30d)	20 (15%)	24 (18%)	0.51
ED Visit (30d)	20 (15%)	24 (18%)	0.51
Hospitalization (30d)	18 (13%)	19 (14%)	0.86
Surgery (30d)	9 (7%)	8 (6%)	0.80
Sensitivity Analysis 90-day)			
Hospitalization-related health care utilization (90d)	30 (22%)	34 (25%)	0.57
ED Visit (90d)	30 (22%)	34 (25%)	0.57
Hospitalization (90d)	27 (20%)	27 (20%)	1.0
Surgery (90d)	11 (8%)	8 (6%)	0.48
Secondary Outcome			
Change in IBD Management, n (%) • Addition of corticosteroids • Change in immunomodulators • Change in biologics	86 (64%) 46 (34%) 27 (20%) 56 (42%)	47 (35%) 27 (20%) 14 (10%) 21 (16%)	**<0.01** **0.03** **<0.01** **<0.01**

[Abbreviations: ED=Emergency Department; IBD=Inflammatory Bowel Diseases]

Table 4.

Factors associated with increased risk of 30-day of hospitalization-related health care utilization based on multivariate logistic regression analysis adjusting for (A) age, prior

	Multivariate*	
Variables	**OR (95% CI)**	**p-value**
Current steroid use	3.09 (1.32 – 7.21)	**0.009**
Current biologic use	0.28 (0.12 – 0.65)	**0.003**
C-reactive protein (per 1mg/dl)	1.11 (1.04 – 1.20)	**0.003**
GI pathogen panel vs. conventional stool testing	3.03 (1.27 – 7.14)	**0.013**
Adding ordering provider as an additional variable		
Current steroid use	2.89 (1.21 – 6.89)	**0.016**
Current biologic use	0.33 (0.14 – 0.78)	**0.011**
C-reactive protein (per 1mg/dl)	1.08 (1.00 – 1.16)	**0.048**
GI pathogen panel vs. conventional stool testing	2.00 (0.81 – 4.95)	0.132
Non-GI providers vs. GI providers	3.73 (1.34 −10.36)	**0.011**

*Multivariate model inclusive of: age and hospitalization within last six months.