

Utility and Recommendations for the Use of Multiplex Molecular Gastrointestinal Pathogen Panels

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Background: Many molecular gastrointestinal pathogen panels (GIPs) are Food and Drug Administration (FDA) cleared but it is still unclear how to best utilize these new diagnostic tools. GIPs are highly sensitive and specific, simultaneously detect multiple pathogens in one reaction, and can shorten the overall time of diagnosis for infectious gastroenteritis but are also expensive with relatively poor insurance reimbursement.

Content: In this review, we take a comprehensive approach to discuss issues with utilization of GIPs from a physician perspective, and implementation from a laboratory perspective. The information presented is to assist physicians in deciding on appropriate use of GIPs in diagnostic algorithms for their patients, and to provide information to laboratories that may be considering the addition of these powerful diagnostic assays to their test menu. Some of the important topics discussed are inpatient vs outpatient use, the appropriate panel size and organisms to include, interpretation of results, laboratory validation, and reimbursement.

Summary: The information in this review provides clear guidance to both clinicians and laboratories in deciding the best use of GIPs for a specific patient population. While this technology provides many benefits over traditional methods, it can also complicate result interpretation and comes with a high cost, which necessitates the need for use recommendations.

INTRODUCTION

Infectious gastroenteritis can be challenging to diagnose given the myriad viral, bacterial, and parasitic pathogens that cause similar symptoms. Patient age, travel history, recent food consumption, vector exposure, and sexual history, as well as symptoms and underlying health conditions,

should be assessed. Laboratory diagnosis has traditionally been limited to culture, microscopy, antigen detection, and singleplex nucleic acid amplification testing (NAAT). Advances in multiplex NAAT technology have resulted in large, multipathogen gastrointestinal panels (GIPs), which simultaneously detect bacterial, viral, and parasitic pathogens. GIPs have rapid turnaround time (TAT)

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IMPACT STATEMENT

The appropriate use of gastrointestinal panels has been an area of confusion for providers and laboratories alike. The exceptional sensitivity, specificity, and turnaround time should make them a welcome addition for the diagnosis of infectious diarrhea, but the high cost and poor insurance reimbursement have limited the use of these panels. The most tangible benefits are for patients with gastrointestinal disease presenting with diarrhea, especially hospitalized or immunocompromised patients, who need a quick diagnosis for proper management. The intent of this article is to provide the key information needed for clinicians and laboratories who are considering the use of GIPs.

and excellent sensitivity and specificity. Given their high cost, there are important issues to consider before implementation of GIPs. In this article, we discuss considerations for clinicians such as using GIP vs traditional diagnostic methods, inclusion of *Clostridioides difficile* on panels, inpatient vs outpatient testing, and overall result interpretation. We will also address concerns of the clinical laboratory such as proper validation, College of American Pathologists (CAP) requirements, confirmatory stool culture, and Current Procedural Terminology (CPT) coding and reimbursement.

TRADITIONAL DIAGNOSTIC METHODS

Stool Culture (Bacterial and Viral)

Stool culture continues to be an important diagnostic test in the clinical microbiology laboratory. Enzyme Immunoassays (EIAs) for antigen detection may also be a useful diagnostic adjunct in some cases (e.g., Shiga toxin, *Campylobacter*). Unformed stool samples are collected and placed into a transport container to preserve organism viability (e.g., Cary-Blair or modified Cary-Blair). The sample must be transported to the laboratory expeditiously to ensure optimal recovery of fastidious organisms such as *Campylobacter* and *Shigella* (1, 2). Since a wide variety of bacterial

pathogens can cause diarrhea, various selective and/or differential media are inoculated to isolate organisms such as *Salmonella*, *Shigella*, and *Campylobacter*. Some organisms such as *Yersinia enterocolitica* require specialized media that are not routinely stocked in most laboratories (3) and others such as *Campylobacter* require unique atmospheric conditions (1). Diagnosis of certain organisms may be missed if not requested by the ordering physician as common media and standard incubation conditions are not sufficient to isolate some stool pathogens (e.g., *Aeromonas*, *Vibrio*). Regardless of these challenges, stool culture is especially important for epidemiological investigations or if antibiotic susceptibility testing is needed. Some viral pathogens may be grown in cell culture, but most clinical laboratories do not offer cell culture options for enteric viruses due to long TAT.

Stool Parasites

Although traditional microscopy in the ova and parasite (O&P) exam has been the mainstay method for identification of stool parasites, there are significant challenges in maintenance of technologist competency, retention of skilled parasitologists, and financial justification to maintain laboratory infrastructure (microscopes and multiple stains). Microscopy is highly dependent upon receiving a quality specimen with a sufficient

number of parasites for visual identification and at morphologically distinct phases of the life cycle. Three separate stool specimens should be collected for optimal sensitivity for detection of clinically relevant parasites; however, this can be challenging in terms of laboratory workflow and patient compliance. Microscopy may not allow for species-level identification within some parasite genera, and multiple staining methods (e.g., trichrome, modified acid-fast) may be needed. The time and labor-intensive nature of these microscopy-based methods often precludes a rapid diagnosis. Alternative methods such as EIAs, biochemical, or serological identification are relatively easy to use and inexpensive but are only available for a limited number of pathogenic species (4).

RECOMMENDATIONS FOR APPROPRIATE USE OF MULTIPLEX NAAT GASTROINTESTINAL PANELS: CONSIDERATIONS FOR CLINICIANS

Considerations for Inpatient vs Outpatient Use

GIP testing has limited utility in most patients for whom the onset of gastrointestinal (GI) symptoms is more than 72 h after hospital admission (5). After this time point, the likelihood of false positivity due to chronic or residual shedding increases. After 5 days post-admission, *C. difficile* should be considered. However, there may be important infection control implications for utilizing GIPs for some inpatients. Use of GIPs was shown to be cost-effective when patients were removed from isolation following negative results, as it reduced days of isolation for patients with non-infectious causes of diarrhea (6). Use of GIPs identifies infectious causes of diarrhea more rapidly and in more patients than conventional methods, resulting in more potentially infectious patients being placed in isolation (7).

For patients seen in an outpatient or emergency room setting, GIPs have been associated with better antibiotic and healthcare utilization. In one study, patients had a reduced length of stay, shorter time to appropriate antimicrobial therapy, and reduced antimicrobial use compared to patients tested with conventional stool culture (8). Additionally, fewer providers prescribed empiric therapy when a GIP was available, and this difference increased with time following panel implementation (8). An example of an improved health outcome due to GIP use is reduced use of antibiotics when rapid detection of Shiga-toxin-producing *E. coli* (STEC) is utilized which lowers the risk of hemolytic uremic syndrome (HUS) (8). GIPs have also been associated with fewer endoscopic procedures and abdominal radiography studies (9). It should be noted that studies regarding the clinical utility of GIPs have been performed in patients whose symptoms are severe enough to seek treatment. Infectious Disease Society of America guidelines only recommend testing when gastroenteritis occurs with fever, bloody stools, severe abdominal pain, or signs of sepsis (10).

Inclusion of *C. difficile* as Part of GIPs

C. difficile, a gram-positive bacillus, is commonly associated with hospital-acquired as well as community-acquired diarrhea and antibiotic use. Infections due to *C. difficile* have been estimated at 500 000 per year in the US with mortality of 15 000 to 30 000 deaths (11). Strains of *C. difficile* that produce enterotoxin (TcdA) and/or cytotoxin (TcdB) result in pseudomembranous colitis (12). *C. difficile* colonizes the GI tract of 5% to 10% of adults with no apparent disease. In addition, up to 60% of infants and young children less than 2 years of age may be colonized, and testing in this population should not be routinely performed (13). *C. difficile* is included on many FDA-cleared GIPs which presents a challenge for result reporting. GIPs cannot differentiate

between colonization and true infection which can result in overdiagnosis of *C. difficile* in patients who may be asymptomatically colonized or immune (14). Most GIPs do not allow end users to choose which targets are reported although recently, the BIOFIRE® FILMARRAY® GI Panel (BioMérieux) has gained FDA approval to mask the *C. difficile* target (15). The identification of this pathogen in a hospitalized patient is considered a hospital-acquired infection and is reportable to the CDC's National Healthcare Safety Network (NHSN) and affects the standardized infection ratio (SIR) score. Hospitals with high *C. difficile* SIR scores are penalized with a reduction of hospital-specific reimbursement by the Center for Medicare and Medicaid Services (16).

Singleplex/Small Panel Testing vs GIP

Single target assays are likely to be useful where risk factors and epidemiological considerations heavily favor one pathogen (*C. difficile* in patients hospitalized for more than 72 h, outbreaks of a pathogen such as Norovirus, exposure to someone with an identified GI pathogen). Beyond these scenarios, multiple pathogens will need to be considered, as vectors of transmission and symptoms of disease overlap (Table 1). Small panels typically target traditional stool culture pathogens and may include other common bacterial and non-bacterial pathogens. Use of these panels in otherwise healthy individuals will identify the most common and clinically actionable causes of infectious diarrhea and may result in better reimbursement from payors.

If a small GIP does not yield a positive result and the patient continues to be symptomatic, or if a patient has risk factors for less common pathogens (immunocompromised status, travel), larger panels may be considered. Positive results from these panels should be interpreted in the context of the patient's clinical condition and risk factors, as these large panels may include targets with

unclear clinical correlation or specific risk factors. Use of panels that include pathogens for which the pre-test probability of infection is low have been associated with false-positive results and pseudo-outbreaks (17). Laboratories may choose to suppress reporting of certain targets in these instances. It is also important to note that the use of GIPs from different manufacturers for a single patient may lead to discrepant results due to potential variations in the limit of detection for a given target.

Result Interpretation: GIP-Positive and Culture-Negative Results

NAAT detects genetic material from both viable and non-viable organisms, which can cause discrepant results between GIPs and stool culture. Interpretation of discrepant results between GIPs and traditional laboratory methods are difficult due to the lack of a singular reference standard for GI pathogens. A conundrum exists as to how clinicians should address NAAT-positive/culture-negative results, as well as NAAT-negative/culture-positive results. A meta-analysis by Freeman and colleagues analyzed agreement between microbiology methods and a GIP (Luminex xTAG®). The authors concluded a high level of negative agreement between both GIP and conventional methods. Virtually all GIP positive cases were confirmed by conventional testing, although certain studies noted a distinct discrepancy in favor of GIPs for the detection of *Salmonella*, *Campylobacter*, and Norovirus. It could not be determined if the detection of additional positives by GIPs were of clinical relevance, or false-positive results. Conversely, when results of conventional methods were compared to GIPs, it could not be determined if sub-optimal detection of Adenovirus by GIPs compared to conventional methods was a function of sampling error, processing error, or the specific Adenovirus assay used in the GIP (35).

There is no question that GIPs allow for accurate and highly specific detection of a variety of GI

Table 1. Common organisms detected on multiplex gastrointestinal molecular panels.^a

Risk Groups				Symptoms					Panels							
				Abdominal												
	Children	Travelers	Immunocompromised	Vector	Nausea/ Vomiting	Fever	Bloody Diarrhea	Non-Bloody Diarrhea	Pain/ Cramping	Other	Verigene	Luminex XTAG	Biofire	BDMax	Applied Qiagen	References
<i>Campylobacter jejuni/coli/spp</i>	X	X		Contaminated food (raw poultry, unpasteurized dairy products), contaminated water	X	X	X	X	X	Gullain-Barré syndrome, reactive arthritis, bacteremia	X	X	X	EBP	X	Centers for Disease Control (18)
<i>Clostridioides difficile</i>	≥2 y.o.		X SOT, HSCT high risk	Fecal-oral exposure Associated with healthcare settings, antibiotic use	X	X	X	X	X	Ileus, megacolon in severe disease	X	X	X	X	X	McDonald et al (11)
<i>Plesiomonas shigelloides</i>		X		Seafood; contaminated water	X		X	X	X	Chronic diarrhea	X	X	X	XBP	X	Janda et al. (19)
<i>Salmonella enterica</i>	X		X	Raw meat, contact with birds and reptiles	X	X	X	X	X		X	X	X	EBP	X	Centers for Disease Control (20)
<i>Yersinia enterocolitica</i>	X			Pork, especially chitlins	X	X	X	X	X		X	X	X	XBP	X	Centers for Disease Control (3)
<i>Vibrio parahaemolyticus/vulnificus</i>		X	X	Shellfish, especially oysters	X	X	X	X	X	Wound/soft tissue infections			X	XBP	X	Centers for Disease Control (21)
<i>Vibrio cholerae</i>		X		Contaminated water	X			X			X	X	X	XBP	X	Centers for Disease Control (22)
Enteraggregative <i>Escherichia coli</i> (EAEC)	X	X	X	Contaminated food, fecal-oral exposure	X	X	X (rare)	X	X	Potential hemolytic uremic syndrome			X	X	X	Croxen et al. (23)
Enteropathogenic <i>E. coli</i> (EPEC)	X	X		Contaminated food/water, fecal-oral exposure	X	X	X	X	X				X		X	Croxen et al. (23)
Enterotoxigenic <i>E. coli</i> (ETEC)	X	X	X	Contaminated food/water, fecal-oral exposure	X	X	X	X	X			X	X	XBP	X	Croxen et al. (23)
Shiga-like toxin-producing <i>E. coli</i> (STEC)	X	X		Contaminated food/water, fecal-oral exposure, Animal contact	X	X	X	X	X	Potential hemolytic uremic syndrome	X	X	X	EBP	X	Croxen et al. (23)
<i>E. coli</i> O157	X	X		Contaminated food/water, fecal-oral exposure, Animal contact	X	X	X	X	X	Potential hemolytic uremic syndrome		X	X	X	X	Croxen et al. (23)
<i>Shigella</i> / Enteroinvasive <i>E. coli</i> (EIEC)	X	X		Contaminated food/water, fecal-oral exposure, person-to-person	X	X	X	X	X	Potential hemolytic uremic syndrome	X	X	X	EBP	X	Croxen et al. (23)
<i>Cryptosporidium</i> sp.	X	X	X	Contaminated water, fresh produce, fecal-oral exposure	X	X	X	X	X	Chronic and severe diarrhea	X	X	X	EPP	X	Centers for Disease Control (24)

Table 1. Continued																		
Risk Groups				Symptoms						Panels								
	Children	Travelers	Immunocompromised	Vector	Nausea/ Vomiting	Fever	Bloody Diarrhea	Non-Bloody Diarrhea	Abdominal Pain/ Cramping	Other	Verigene	Luminex xTAG	Biofire	BDMax	Applied Biocode	Qiagen	References	
<i>Cyclospora cayotensis</i>	X	X	X	Contaminated water, fresh fruits, leafy greens	X	X		X	X	Symptoms may wax and wane			X			X	Almeria et al. (25), Centers for Disease Control (26)	
<i>Entamoeba histolytica</i>	X	X	X	Contaminated water, fresh produce, fecal-oral exposure		X	X		X	Liver abscess in severe infections		X	X		EPP	X	X	Centers for Disease Control (27)
<i>Giardia duodenalis</i> (intestinalis, lamblia)	X	X	X	Contaminated water; fresh produce, fecal-oral exposure	X	X		X	X	Flatulence, steatorrhea		X	X		EPP	X	X	Centers for Disease Control (28)
Adenovirus 40/41	X		X	Fecal-oral exposure, close-contact settings; ^b transplacental tissue (small bowel, liver)	X	X		X	X			X	X		EVP	X	X	Ison et al. (29)
Astrovirus	X		X	Contaminated water; fecal-oral exposure, close-contact settings	X	X		X	X	Headache			X		EVP	X	X	Johnson et al. (30)
Norovirus GI/GII	X	X	X	Contaminated food/ water, fecal-oral exposure, close-contact settings	X	X		X	X	Persistent disease and viral shedding in HSCT and SOT recipients	X	X	X		EVP	X	X	Roblotti et al. (31)
Rotavirus	X	X	X	Contaminated food/ water, fecal-oral exposure, close-contact settings	X	X		X	X		X	X	X		EVP	X	X	Crawford et al. (32)
Sapovirus	X	X	X	Contaminated water; fecal-oral exposure, close-contact settings	X			X	X				X		EVP		X	Oka et al. (33), Daniel, Wayman et al. (34)

^aAbbreviations: X, characteristic present; EBP, enteric bacterial panel; y.o., year old; SOT, solid organ transplant; HSCT, hemopoietic stem cell transplant; XBP, extended enteric bacterial panel; EVP, enteric viral panel; SCID, severe combined immunodeficiency.

^bClose-contact settings: daycare, extended-care facilities, military barracks, dormitories, hospitals.

pathogens. It is important to remember that detection by GIP does not necessarily equate with actual disease caused by the pathogen(s) detected. Results of GIPs must always be evaluated in context with other clinical findings. Pathogens may be transient colonizers of the GI tract or shed for long periods of time after a confirmed infection (31). Nucleic acid of non-viable organisms can be detected after infection has resolved and as such, GIPs should not be employed as a “test of cure.” Recent vaccination history should also be evaluated because patients can shed Rotavirus post-vaccination which in some cases could be detected by GIPs (32). It can be difficult for clinicians to know which organism is the causative agent of the patient’s current symptoms, potentially affecting appropriate treatment. Laboratories should maintain options for confirmatory culture testing in instances when GIP results may be called into question or further characterization is needed to guide treatment.

CONSIDERATIONS FOR LABORATORIES PERFORMING MULTIPLEX GIP

Laboratories considering a GIP should be aware of requirements related to validation and maintenance of these assays. If the lab is CLIA-certified, there are requirements in the microbiology CAP checklist (36) related to multiplex molecular assays. As these panels contain large numbers of targets, it is not acceptable to use a QC material for just one organism on the panel but impractical to use a separate control for every organism. As of the time of this publication, the requirement is that a control for every analyte is included on each run (multiplex QC) or rotated among runs so that periodically, all organisms on the panel are tested (36). The CAP does allow for laboratories to reduce the amount of QC performed through implementation of an individual quality control plan (IQCP). Another requirement

is related to cross-checks of new lots and shipments of reagent which are normally performed using previously tested patients and/or control material for the testing analyte. For multiplex tests, at least 2 organisms on the panel must be included for each new lot or shipment cross-check, and these 2 analytes must be rotated periodically (36). The laboratory needs to have a written procedure for how these requirements will be addressed, and the specific analyte(s) used for external QC and cross-checks should be documented to demonstrate compliance with these requirements. Additionally, laboratories must monitor for nucleic acid contamination when using molecular microbiology tests in order to detect possible false-positive results (36). Following best practices in the molecular laboratory will reduce the risk of contamination, but proactive monitoring should be done via routine environmental testing as well as by monitoring normal clinical positivity rates, unusual clinical results, and investigating any outlier data.

Another challenge with adopting a GIP in the clinical laboratory relates to the validation or verification of the assay in the clinical laboratory. It can be difficult to obtain positive patient samples for all pathogens on the panel, especially for rare organisms. In this case, spiking patient matrix (stool) with whole organism can be an acceptable alternative. If the test is FDA-cleared, the laboratory can perform a laboratory verification with patient or contrived samples representing all the pathogens on the GIP. Modification of FDA-cleared assays can prove especially challenging for multiplexed panels since a full analytical validation would be required for all pathogens on the panel. The most common specimen type for FDA-cleared GIPs in stool is Cary-Blair. Laboratories should take special care in validating any other sample types not specifically listed in the manufacturer instructions, such as raw stool with no transport media or rectal swabs. While this section refers mainly

to CAP requirements, laboratories with different accreditations or outside of the US should be aware that validation and regulatory requirements may differ.

Confirmatory Culture for Bacterial Pathogens for Susceptibility Testing and Public Health Requirements

Clinical laboratories now have the option to phase out bacterial stool culture/ O&P exams due to widespread availability of GIPs. Although reduction of these services may reduce laboratory operating costs and competency requirements, culture-based confirmation of a positive bacterial result may be required to determine antibiotic susceptibility and to fulfill public health requirements. Bacterial culture is also required for detection of organisms that are not included on GIPs such as *Campylobacter ureolyticus*, or serogroup-level identification of *Salmonella*. The ability to perform culture-dependent techniques on isolates of organisms such as *Salmonella*, *Campylobacter*, and *Shigella* may be essential for patient care, investigations of food-borne illnesses, and monitoring for disease outbreaks. Patterns of antimicrobial susceptibility can be used in conjunction with subtyping information to provide useful information to link incidence of illness to specific sources or to detect emerging patterns of antimicrobial resistance (37). In most states, organisms are cultured by the clinical microbiology laboratory and submitted to a public health laboratory for species-level identification, molecular subtyping, serotyping, or whole-genome sequencing. All these activities are dependent upon a pure bacterial culture as starting material for further characterization. There are concerns that use of GIPs replacing bacterial culture will limit access to isolates, ultimately reducing the capability of public health laboratories to investigate disease outbreaks (10). Due to inherent differences in the scope of services offered by clinical laboratories (e.g.,

disease diagnostics), and public health laboratories (e.g., disease surveillance), most public health laboratories do not have the workflow infrastructure to support culture, isolation and characterization of large numbers of clinical samples. Although submission of culture isolates is currently mandated by a majority of state and territorial public health departments, the concern is that clinical laboratories using GIPs will not perform reflex culture on positive samples in an attempt to save costs of culture reagents and personnel needed for specimen submission (38). From a public health perspective, these issues were discussed by Cronquist et al. with the conclusion that outbreak investigations, disease investigations for case control, and disease trend analysis could be significantly affected by wide-scale implementation of culture-independent GIPs. A recommendation to codify adequate funding for public health surveillance activities and assure isolate submission by sentinel surveillance laboratories was also proposed (37). For laboratories who choose to implement GIP, several considerations related to culture requirements must be considered. Timely culture inoculation by the collecting clinical laboratory is ideal, as delays in stool specimen processing is known to adversely affect recovery of labile organisms such as *Campylobacter* sp. or *Escherichia coli* non-O157 (38). The laboratory should also consider the requirement for confirmatory culture when publishing specimen requirements for GIP. Several GIPs accept unpreserved stool (BD Max™, Luminex xTag), which is not conducive to culture after the completion of GIP testing. Raw stool should be placed into a preservative like Cary-Blair, ideally within 2 h after collection, to maintain organism viability (2). For this reason, laboratories should consider only accepting samples in preservative unless the laboratory itself has a mechanism to add the raw stool to Cary-Blair within hours of collection. If culture setup is delayed, fastidious organisms such as *C. jejuni* or *Shigella* species may

not be recovered, which could explain some GIP-positive/culture-negative results (2). Another budgetary concern is that the clinical laboratory will not be eligible for insurance reimbursement for this culture, as reflex stool culture would be considered an ancillary activity and not the primary diagnostic method.

CPT Coding and Current Payor Landscape for GIP

The Current Procedural Terminology (CPT) system is a patented, standardized coding system for medical procedures and services, which was developed by the American Medical Association (AMA) in 1996. This system allows for coding and describing healthcare procedures (including laboratory tests) for use by Medicare, Medicaid, private healthcare providers, and commercial insurers (39). Specific CPT codes are available for GIPs. The code used depends on the number of targets detected (≤ 5 , 6 to 11, 12 or more), and pertinent underlying conditions such as immunosuppression (40). Proprietary laboratory analyses (PLA) codes may also be used for identification of a specific test if requested by a manufacturer or clinical laboratory and approved by the AMA PLA Technical Advisory Group and CPT Editorial Panel (41).

Currently, the costs of laboratory services are covered by the Medicare part B program as administered by the US Centers for Medicare and Medicaid Services (CMS) (41). Laboratory tests are reimbursed under the Clinical Laboratory Fee Schedule (CLFS), which is updated every 3 years, and includes a forum for public comment on fee changes. Although CMS is the governmental payor, the CLFS has significant influence over the coverage and payment policies of private commercial payors. Seven private companies contract with CMS to oversee processing of claims, including laboratory services. Furthermore, the Molecular Diagnostic Services (MoDx) program evaluates clinical utility and validity of molecular

tests to establish coverage and reimbursement of laboratory charges (also known as Local Coverage Determination, LCD). Palmetto GBA is the Medicare administrative contractor (MAC) which oversees the MoDx program, but many other MACs use the Palmetto GBA recommendations to set coverage for diagnostic tests and pricing (41).

In 2017, Palmetto GBA drafted limited coverage for GIPs to specific bacterial targets only (*Salmonella*, *Campylobacter*, *Shigella*, *Cryptosporidium*, STEC O157, STEC non-O157), with no coverage for viral testing or other parasites contained on panels. These targets are a fraction of the total number and types of targets detectable by most current GIPs. In a coordinated effort, multiple professional societies such as the Association for Molecular Pathology (AMP), American Society for Microbiology (ASM), Association of Public Health Laboratories (APHL), CAP, Infectious Diseases Society of America (IDSA), American Gastroenterological Association (AGA), and the Pan American Society for Clinical Virology (PASCV) strongly recommended modification of the coverage determination to >5 targets in order to reflect the breadth and diagnostic utility of larger GIPs when used in conjunction with specific disease presentations and patient history (42). Under an LCD revision dated 3/4/2021, coverage of GIPs is still limited to the 5 bacterial targets in immunocompetent patients. However, a modification was made to allow coverage for 6 to 11 targets if *C. difficile* is included, and 12 or more targets if needed for an immunosuppressed or critically ill patient. Coverage for viral GI pathogens only, community-acquired diarrheal illness, or epidemiologic assessment of outbreaks is currently denied (40). Clearly the issue of responsible utilization of and reimbursement for GIPs is still a matter of considerable debate with broad implications as manufacturers are bringing panels with higher number of targets to market.

CONCLUSION

GIPs are an emerging technology that have potential to improve diagnosis of infectious diarrhea but are not a direct replacement of the gold standard of stool culture. Both have a place in the diagnostic landscape due to the complex nature of the condition and various modes of acquisition, causative agents, and susceptible populations. While GIPs are superior to stool culture in many ways, such as sensitivity, TAT, and viral detection, stool culture is required for detecting viable bacterial organisms and allowing for determination of antibiotic susceptibility and epidemiological studies. GIPs may be particularly useful in immunocompromised or

hospitalized patients (with diarrhea <5 days) or when results for stool culture or smaller panels do not identify the causative agent. Single-target or smaller panels are also useful, such as *C. difficile* assays for longer-term hospitalized patients or during outbreaks of a particular virus. Each institution must weigh the benefits and drawbacks as well as consider their patient population before deciding which assays are appropriate, keeping in mind that if a GIP-only model is adopted, options for culture confirmations should be considered. As the technology becomes more widely adopted and more publications demonstrate their utility, issues related to reimbursement will also need to be addressed to ensure that laboratories are incentivized to offer the assays.

Nonstandard Abbreviations: GIP, gastrointestinal pathogen panel; NAAT, nucleic acid amplification testing; CAP, College of American Pathologists; GI, gastrointestinal.

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