University of Nebraska Medical Center
REGIONAL PATHOLOGY SERVICES

LAB ALERT

Date: December 4, 2014

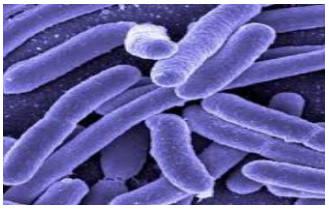
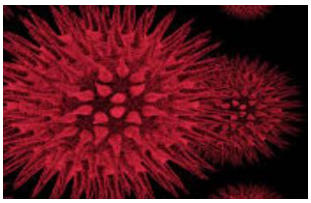
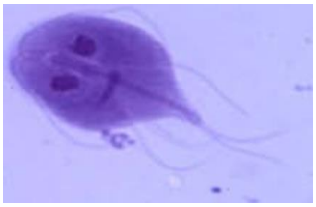
RE: New Molecular Based Gastrointestinal Panel that Detects 21 Targets Simultaneously

Dear Regional Pathology Clients,

We are very excited to announce that effective January 6, 2015, the Clinical Microbiology Laboratory will introduce a new FDA-approved molecular test, the Gastrointestinal [GI] Pathogen Panel for detection of bacterial, viral, and parasitic pathogens from stool. The GI Pathogen Panel is a nested multiplex polymerase chain reaction test to qualitatively detect and identify common GI pathogens.

Use of this molecular panel will significantly decrease reporting of fecal pathogens from 3-5 days to less than 8 hours and will increase testing sensitivity and the ability to isolate multiple GI pathogens using **ONE** test. In addition, the ability to recover certain pathogens, such as pathogenic *E. coli* pathotypes, is new.

The Table below lists all the targets that will be reported under the new GI Panel:

Bacteria 	• *Campylobacter* sp. • *Plesiomonas shigelloides* • *Salmonella* sp. • *Yersinia enterocolitica* • *Vibrio* sp. • *Vibrio cholera* • Enteroaggregative *E. coli* (EAEC) • Enteropathogenic *E. coli* (EPEC) • Enterotoxigenic *E. coli* (ETEC) • Shiga-like toxin producing *E. coli* (STEC) *stx1/stx2* • *E. coli* 0157 • *Shigella*/Enteroinvasive E. coli (EIEC)
Viruses 	• Adenovirus F 40/41 • Astrovirus • Norovirus GI/GII • Rotavirus A • Sapovirus
Parasites 	• *Cryptosporidium*, • *Cyclospora cayetanensis*, • *Entamoeba histolytica* • *Giardia lamblia*.

This panel will replace traditional stool culture (STOCU) and *Giardia* and *Cryptosporidium* antigen screen (OVPSC) as well as individual cultures for *Yersinia* (YERCU) and *Vibrio* species (VIBCU). Interfaced Clients: Please remove these codes from your interfaces.

The GI Pathogen Panel results will be reported as "detected" or "not detected." Isolation cultures will be automatically ordered for specimens positive for *Campylobacter* and *Shigella* to allow for susceptibility testing of these isolates. Recovery cultures for other pathogenic bacteria identified by the GI Pathogen Panel may be performed upon physician request and approval by the laboratory director.

Please note that at this time testing for rotavirus antigen (ROTA) and full Ova & Parasite examination (OVPAR) will be maintained. In addition, the Molecular Diagnostics Laboratory will maintain current testing for Adenoviruses (ADVBL and ADVOT) and Noroviruses (NVDET) including subtyping for Norovirus GI and GII.

Specimen Requirements: Enteric Plus or Cary Blair Transport Medium. Fresh stool not in transport will be added to the medium prior to testing, however, it must be received into the laboratory within 2 hours of collection.

Rejection Criteria: Stool specimens in fixative or transport medium other than Enteric Plus or Cary Blair.

Turn-around Time: Performed daily and reported on same shift; 24 hours during outbreaks.

Treatment Recommendations: The Infectious Disease team at Nebraska Medicine has developed these guidelines. Refer to document attached below.

Panel CPT Code: 87507

Interfaced Clients: These codes need to be built in the interfaces.

Order Code:	**GIP**		
Order Name:	**GI PATHOGEN PANEL**		
LIS Order Code	**Result codes**	**Order/Result Name**	**Order/Result Full Name**
CMPY	CMPY	Campylobacter sp.	Campylobacter species
PLESI	PLESI	Plesiomonas sp.	Plesiomonas shigelloides
SLMSP	SLMSP	Salmonella species	Salmonella species

VBRSP	VBRSP	Vibrio species	Vibrio species
VBRC	VBRC	Vibrio cholerae	Vibrio cholerae
YRSE	YRSE	Y. enterocolitica	Yersinia enterocolitica
EAEC	EAEC	E. coli (EAEC)	Enteroaggregative E. coli (EAEC)
EPEC	EPEC	E. coli (EPEC)	Enteropathogenic E. coli (EPEC)
ETEC	ETEC	E. coli (ETEC)	Enterotoxigenic E. coli (ETEC) lt/st
STEC	STEC	E. coli (STEC)	Shiga-like producing E. coli (STEC) stx1/stx2
ECO157	ECO157	E. coli O157	E. coli O157
EIEC	EIEC	Shigella (EIEC)	Shigella/Enteroinvasive E. coli (EIEC)
CRYPTO	CRYPTO	Cryptosporidium	Cryptosporidium species
CAYE	CAYE	C. cayetanensis	Cyclospora cayetanensis
EHISTO	EHISTO	E. histolytica	Entamoeba histolytica
GLAMB	GLAMB	Giardia lamblia	Giardia lamblia
ADNVF	ADNVF	Adenovirus F 40/41	Adenovirus F 40/41
ASTRV	ASTRV	Astrovirus	Astrovirus
NOROV	NOROV	Norovirus GI/GII	Norovirus GI/GII
ROTVA	ROTVA	Rotavirus A	Rotavirus A
SAPO	SAPO	Sapovirus	Sapovirus
GIPCOM	GIPCOM	Comment	GIP Comment

If Shigella or Campylobacter are detected with the GI Panel, patient susceptibility testing must be ordered. The Client will be called to order these.

The following susceptibility codes need to be built in the interfaces:

ORGSS=GIP Organism Isolation Culture 1 (Shigella reflex susceptibilities from GIP panel and Salmonella by

request)

ORGISO=GIP Organism Isolation Culture 2 (Campylobacter reflex susceptibilities from GIP panel and other bacterial targets on the panel by request-other than Shigella/Salmonella).

2015 Panel CPT Code: 87507

For questions about this lab alert or for pricing and reimbursement please contact the Client Coordinators, Brian Lenz, blenz@unmc.edu or Dana El-Hajjar, delhajja@unmc.edu

For technical questions please contact Paul D. Fey, Ph.D., Laboratory Director, at (402) 559-2122 or Amy Crismon, Microbiology Manager, at (402) 552-3313, or by calling the Clinical Microbiology Laboratory at (402) 552-2090.

Gastrointestinal Panel Guidance

Authors: Kiri Rolek, PharmD, BCPS, Paul Fey PhD, Mark Rupp, MD, and Trevor Van Schooneveld, MD

Background:

Many pathogens, including bacteria, parasites, and viruses can cause infectious diarrhea. Previously, many of the pathogens responsible could only be isolated using traditional techniques such as stool culture or ova and parasite exam that were often time consuming and lacked sensitivity. To improve the detection of intestinal pathogens, the microbiology lab has introduced multiplex PCR testing using the FilmArray Gastrointestinal (GI) panel, which detects 22 common viruses, bacteria, and parasites that cause infectious diarrhea. Results are typically available in about one hour.

Testing:

This panel will replace traditional stool culture (STOCU) and the *Giardia* and *Cryptosporidium* antigen (OVPSC) screen. Stool cultures with isolation and susceptibility will now only be obtained reflexively when *Shigella* and *Campylobacter* are detected by the GI panel. The stool Ova & Parasite microscopic test (OVPAR), used primarily for individuals with a history of travel to foreign countries, will still be available but should be reserved for those who have **both** clinical symptoms and an epidemiologic exposure strongly suggestive of a parasite not detected by the GI Panel.

C. difficile testing is part of the panel but will not be reported. The reason for this is the microbiology lab and antimicrobial stewardship team have determined that PCR testing alone is inadequate for accurately identifying those with *C. difficile* infection (CDI) who require treatment.[1,2] If CDI is suspected the *C. difficile* toxin assay is recommended as it is the preferred method to diagnose CDI. In cases where the GI panel *C. difficile* PCR is positive and no *C. difficile* test has been ordered the microbiology lab will contact the clinician so they can decide if further testing for CDI is warranted.

Restriction:

The GI panel may only be ordered for patients who have been hospitalized for less than 5 days; otherwise it will require approval from the microbiology director (or their designee) who will consult with the antimicrobial stewardship program or the infectious disease service when needed. The panel may also only be ordered once per admission. These restrictions will be put in place as data show that routine stool cultures from patients with diarrhea that develops after 72 hours of hospitalization are typically low yield for standard bacteria and parasites.[3,4]

Interpretation:

Results of PCR testing for stool pathogens must be taken into clinical context when making treatment decisions. Previously treatment decisions were made based upon either clinical presentation or traditional microbiologic diagnostic techniques. PCR testing is much more sensitive than traditional techniques and allows for the detection of low numbers of pathogens.[5,6,7] The clinical correlation of PCR results with the need for treatment and clinical outcomes has not been established. Studies evaluating

stool PCR testing frequently detect more than one enteric pathogen in patient's stool and data are not available to determine the causative organism in these situations.[5,7] Additionally low levels of stool pathogens have been detected in healthy persons and all decisions regarding need for treatment must be taken into clinical context of the patient.

Treatment Recommendations:

Taking all this into account most gastrointestinal infections due to common bacterial and viral causes are self-limited in nature and do not require antimicrobial therapy. Symptoms typically resolve within 7 days in a normal host and therapy should focus on providing supportive care by replacing fluid and electrolyte losses. The use of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences, including antimicrobial-resistant infections, side effects of treatment with antimicrobial agents, super-infections when normal flora are eradicated by antimicrobial agents, the prolongation of a carrier state (particularly in *Salmonella*) and the possibility of induction of disease-producing phages by antibiotics (such as Shiga-toxin phage induced by quinolone antibiotics).

The role of antimicrobial therapy depends on the implicated pathogen. In general, antimicrobial agents are only used to treat parasitic infections as well as select bacterial infections. Misuse and overuse of antibiotics in the treatment of diarrheal illness has played an important role in the development of drug resistance, which complicates treatment of those infections in which antibiotics are indicated. Listed below are suggested criteria for treatment of specific pathogens. These recommendations apply to generally healthy persons unless otherwise noted. There is a paucity of data regarding the efficacy of antimicrobials in a number of the pathogens detected on the panel and in these cases antibiotics are generally only recommended in severe or non-resolving cases or those at risk for severe disease such as immunocompromised patients. Areas where antibiotics are always indicated have been delineated as has areas where the data are less clear. In cases where data are lacking, clinical judgment and the assessment of the risk verses benefit ration must be considered.

Table 1 – Etiology and Treatment Recommendations[8,9,10,11]

Pathogen	Common Presentation	Commonly Implicated Sources and Seasonality	Treatment Recommendations	Antibiotics (If Indicated)
Bacteria				
Campylobacter	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present	Poultry, unpasteurized milk and dairy products Peak season – spring, summer	Most patients recover without antimicrobial therapy. Antibiotics have been shown to reduce symptom duration by 1.3 days and are recommended for severe illness (high fever, bloody, severe, or worsening diarrhea) or risk factors for complications (elderly, pregnant women, immunocompromised).	Azithromycin 500 mg daily x 3 days Fluoroquinolone x 3 days* Immunocompromised patients may require prolonged therapy (7-14 days)
Clostridium difficile (toxin A/B)	More than 3 watery, loose, or unformed stools within 24 hours; lab findings may include leukocytosis and elevated creatinine	Recent antibiotic use, especially broad spectrum agents	Test not reported on panel. If CDI is suspected, order the *C. difficile* toxin assay.	Metronidazole 500 mg TID x 10-14 days Vancomycin 125 mg QID x 10-14 days See CDI treatment algorithm Discontinue antibiotics if possible www.nebraskamed.com/asp
Plesiomonas shigelloides	Severe abdominal cramps, and diarrhea within 6-48 hours	Fresh water, shellfish, international travel	Most patients recover without antimicrobial therapy. Unclear if antibiotics shorten the duration of illness. Consider in severe diarrhea, extremes of age, and immunocompromised.	Fluoroquinolone x 3 days* Azithromycin 500 mg daily x 3 days TMP/SMX DS BID x 3 days
Salmonella	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present	Poultry, eggs, dairy products, produce, reptile contact Peak season – summer, fall	Antibiotics have no significant effect on the length of illness and may prolong carriage of the organism in the stool. Antibiotics should generally be avoided but recommended for severe illness (>8 stools/day, high fever, hospitalized) or risk for complications (age <1 or > 50, immunocompromised)	Antibiotics typically not indicated Fluoroquinolone x 7 days* Azithromycin 500 mg daily x 7 days TMP/SMX DS BID x 7 days Immunocompromised patients require 14 days of therapy or longer if relapsing
Yersinia enterocolitica	Fever and abdominal cramps within 1-11 days, with or without diarrhea, fecal leukocytes often present	Unpasteurized milk, undercooked pork, chitterlings Peak season – winter	Most patients recover without antimicrobial therapy. Unclear if antibiotics shorten the duration of illness.	Antibiotics typically not indicated For immunocompromised patients, doxycycline 100 mg IV BID + tobramycin or gentamicin 5 mg/kg/day (TMP/SMX, FQs are alternatives)
Vibrio species	Fever, abdominal	Shellfish	Most patients recover without antimicrobial	Azithromycin 1 g x 1 dose Doxycycline 300 mg x 1 dose

(if positive and *V. cholera* negative indicates *V. parahaemolyticus* or *V. vulnificans* is present)	cramps, and diarrhea within 6-48 hours, fecal leukocytes often present		therapy. Unclear if antibiotics shorten the duration of illness. Consider in severe or prolonged diarrhea.	
Vibrio cholerae	Abdominal cramps and large volume watery diarrhea within 16-72 hours	Shellfish, travel to Haiti or other areas where cholera is endemic	Oral rehydration is the key intervention. Antibiotics shorten the duration of illness and are recommended.	Azithromycin 1 g x 1 dose Doxycycline 300 mg x 1 dose Levofloxacin 500 mg x 1 dose Ciprofloxacin 500 mg x 1 dose
Diarrheagenic E. coli/Shigella				
Enteroaggregative *E. coli* (EAEC)	Abdominal cramps and watery diarrhea within 16-72 hours, can be prolonged	International travel, infantile diarrhea in developing countries	Limited data in EAEC and EPEC. Many patients recover without antimicrobial therapy. Antibiotics have been shown to shorten the duration of illness in ETEC and are generally indicated for moderate to severe diarrhea (>4 stools/day, fever, or blood or pus in stool).	Fluoroquinolone x 3 days* Rifaximin 200 mg TID x 3 days Azithromycin 1 g x 1 dose or 500 mg daily x 3 days
Enteropathogenic *E. coli* (EPEC)				
Enterotoxigenic *E. coli* (ETEC) *lt/st*				
Shiga-like toxin-producing *E. coli* (STEC) *stx1/stx2* (shiga-toxin producing *E. coli* is present)	Bloody diarrhea with minimal fever within 3-8 days	Unpasteurized milk, fresh produce, ground beef, petting zoos	**Antibiotics and antimotility agents should be avoided.** Antibiotics have no effect on duration or severity of symptoms and certain antibiotics may increase the risk for hemolytic-uremic syndrome.	Supportive care only
E. coli O157 (the shiga-toxin producing *E. coli* is type O157)				
Shigella/Enteroinvasive *E. coli* (EIEC)	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes present	Egg salad, lettuce, day care	Treatment is recommended if detected.	TMP-SMX 160-800 mg BID x 3 days Fluoroquinolone x 3 days* Immunocompromised patients with *Shigella* require 7-10 days of therapy

*Levofloxacin 500 mg daily or ciprofloxacin 500 mg BID

Table 1 (cont.) – Etiology and Treatment Recommendations[8,9,10,11]

Parasites				
Cryptosporidium	Prolonged watery diarrhea	Contaminated water (recreational and drinking), unpasteurized apple cider	Most patients recover without antimicrobial therapy but antibiotics may decrease the duration of illness. Immunocompromised patients often develop prolonged symptoms and respond poorly to therapy.	May use antimotility agents and/or nitazoxanide 500mg BID x 3 days for prolonged or severe illness ID consult recommended for immunocompromised patients
Cyclospora cayetanensis		Imported fresh produce	Treatment indicated if symptomatic.	TMP/SMX DS BID x 7-10 days

				ID consult recommended for immunocompromised patients
Entamoeba histolytica		Returning travelers	Treatment recommended if detected.	Metronidazole 500 mg TID x 7-10 days OR Tinidazole 2 g daily x 3 days OR Nitazoxanide 500 mg PO BID x 3 days followed by paromomycin 25 mg/kg/day in 3 divided doses x 7 days
Giardia lamblia		Contaminated recreational water, daycare, international travelers	Treatment indicated if symptomatic.	Tinidazole 2 g x 1 dose Nitazoxanide 500 mg PO BID x 3 days Metronidazole 500 mg TID x 5-7 days
Viruses				
Adenovirus F 40/41	Vomiting and non-bloody diarrhea within 10-51 hours	Children <2 yrs, day care	No therapy available. Treat symptomatically.	Antibiotics not indicated
Astrovirus		Children <1 yr, day care		
Norovirus GI/GII		Salads, shellfish, cruise ships, epidemic foodborne disease Peak season – winter		
Rotavirus A		Infants Peak season – winter		
Sapovirus		Children		

Table 2 – Pediatric Dosing Recommendations

Agent	Recommended Dosing
Azithromycin	10 mg/kg daily
Ciprofloxacin*	20-30 mg/kg/day in 2 divided doses (max 1.5 g/day)
Doxycycline	≥ 8 years: 2-4 mg/kg/day divided every 12-24 hours (max 200 mg/day)
Levofloxacin*	< 5 years: 8-10 mg/kg/dose twice daily ≥ 5 years: 10 mg/kg/dose once daily (max 750 mg/day)
Metronidazole	Giardiasis: 15 mg/kg/day in divided doses every 8 hours (max 250 mg/dose) *C. difficile*: 30 mg/kg/day in divided doses every 6 hours (max 2000 mg/day)
Nitazoxanide	1-3 years: 100 mg every 12 hours 4-11 years: 200 mg every 12 hours ≥ 12 years: 500 mg every 12 hours
Paromomycin	25-35 mg/kg/day divided every 8 hours
Rifaximin	3-11 years: 100 mg four times daily (limited data) ≥ 12 years: 200 mg three times daily
Tinidazole	50 mg/kg single dose or daily (max 2000 mg/day)
TMP/SMX	≥ 2 months: 8-10 mg/kg/day (TMP component) in divided doses every 12 hours
Vancomycin (oral)	40 mg/kg/day PO divided every 6-8 hours

*Fluoroquinolones are not routinely used as first line therapy in pediatrics

References:

1. Dionne LL, Raymond F, Corbeil J, et al. Correlation between *Clostridium difficile* bacterial load, commercial real-time PCR cycle thresholds, and results of diagnostic tests based on enzyme immunoassay and cell culture cytotoxicity assay. *J Clin Micro*. 2013;51:3624-30.
2. Planche TD, Davies KA, Coen PG, et al. Differenes in outcomes according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C. difficile* infection. *Lancet Infect Dis*. 2013;13:936-45.
3. Rohner P, Pittet D, Pepey B, et al. Etiological agents of infectious diarrhea: implications for requests for microbial culture. *J Clin Microbiol* 1997; 35:1427.
4. Bauer TM, Lalvani A, Fehrenbach J, et al. Derivation and validation of guidelines for stool cultures for enteropathogenic bacteria other than Clostridium difficile in hospitalized adults. *JAMA*. 2001;285(3):313-319.
5. Khare R, Espy MJ, Cebelinski E, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. *J Clin Micro*. 2014;52:3667-73.
6. Liu J, Kabir F, Manneh J, et al. Development and assessment of molecular diagnostic tests for 15 enteropathogens causing childhood diarrhoae: a multicentre study. *Lancet Infect Dis*. 2014;14:716-24.
7. Kabayiza JC, Andersson ME, Nilsson S, et al. Real-time PCR identification of agents causing diarrhea in Rwandan children less than 5 years of age. *Pediatr Infect Dis J*. 2014;33:1037-42.
8. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis.* 2001;32:331-50.
9. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, eds. *The Sanford Guide to Antimicrobial Therapy*, 39th ed. Sperryville, VA: Antimicrobial Therapy, Inc; 2014.
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