

Guidance for use of the Gastrointestinal Panel (GIPAN)

This assay is a multiplex real-time PCR assay that is available for outpatient testing and inpatient testing within 3 days of hospitalization. For inpatients, this test replaces stool culture, and antigen testing for *Giardia*, Shiga toxin, Rotavirus and Adenovirus 40/41. If parasitic infection is suspected that is not included in this assay, ova and parasite examination can be ordered. This test should not be used as the primary means to diagnose *C. difficile*. This assay is highly sensitive and may detect more than one pathogen in some patients. Clinical correlation with results is critical for proper test interpretation and patient management.

Target	Interpretation	Testing Limitations
<i>Clostridium difficile</i>	<p>Positive: Toxigenic <i>C. difficile</i> DNA detected. This may indicate infection, colonization, or treated infection. If the patient presentation is consistent with infection, no further testing is required.</p> <p>Negative: No <i>C. difficile</i> present. No further testing is indicated.</p> <p>Positive and <i>Clostridium difficile</i> (<i>C. diff</i>) by EIA (two-step EIA/PCR test) is ordered: If the EIA/PCR assay is positive, toxigenic <i>C. difficile</i> is present and the patient should be managed according to UMHS guidelines. However, if negative, the possibilities of infection, colonization or treated infection remain and clinical judgment is required.</p>	<p>Due to the high asymptomatic carriage rates, especially in young children < 12 months of age, the clinical relevance of the detection of toxigenic <i>C. difficile</i> from stool should be considered in the context of other clinical findings, patient age, and risk factors including hospitalization and antibiotic exposure.</p>
<i>Diarrheagenic E. coli/Shigella</i>		
Enteropathogenic <i>E. coli</i> (EPEC)	EPEC is commonly associated with travelers diarrhea. Asymptomatic carriage may occur. Peak incidence in warmer months.	Typical and atypical variants are detected, however not differentiated. The FilmArray™ GI Panel cannot distinguish between certain STEC strains and a co-infection of EPEC and STEC. When STEC is present, EPEC reported as "NA"
Enterotoxigenic <i>E. coli</i> (ETEC)	Most common cause of traveller's diarrhea. Asymptomatic carriage may occur. Interpretation of a positive result requires assessment of the patient's age, clinical presentation and recent travel history.	Potential cross reactivity (causing false positivity) with other GI flora.
Enteraggregative <i>E. coli</i> (EAEC)	Associated with both travellers and non-travellers diarrhea. It is more common in children and also noted to be a cause of persistent diarrhea among HIV positive patients. It has been identified as the cause of large outbreaks worldwide. Interpretation of a positive result requires assessment of the patient's age, clinical presentation and recent travel history.	The assay detects two targeted genes located on pAA plasmid. Not all variants are detected, however most pathogenic strains, including O104:H4, are detected.

Shiga-like toxin-producing <i>E. coli</i> (STEC), including <i>E. coli</i> O157.	High risk groups include age extremes, and individuals that may have ingested contaminated beef or dairy. Antibiotic treatment may increase risk of hemolytic-uremic syndrome (HUS) due to upregulation of toxin production. <i>STEC infections (including E. coli O157) are notifiable diseases to the health department.</i>	The <i>E. coli</i> O157 result is only reported in association with STEC stx1/stx2. When stx is not detected, O157 result is "NA". The assay cannot distinguish between O157 and co-infection of STEC non-O157 and stx-negative O157 (rare). Stx1 is found in <i>S. dysenteriae</i> , as a result STEC and EIEC positivity in a single sample may indicate <i>S. dysenteriae</i> .
Shigella/Enteroinvasive <i>E. coli</i> (EIEC)	Associated with contaminated food or water. Common in regions or situations where hygiene is compromised (e.g. daycares, nursing homes); endemic in regions with no running water or plumbing. EIEC is rare in the US. <i>Shigellosis is a notifiable disease to the health department.</i>	The detection of both Shigella/Enteroinvasive <i>E. coli</i> (EIEC) and STEC stx1/stx2 analytes in the same specimen may indicate the presence of <i>S. dysenteriae</i> .
Bacteria		
<i>Plesiomonas shigelloides</i>	<i>P. shigelloides</i> gastroenteritis often follows consumption of seafood, as well as contaminated water used for drinking or used in preparing uncooked foods.	Single assay for <i>P. shigelloides</i> , the only known species in the genus <i>Plesiomonas</i> . No known limitations specific for this assay
<i>Salmonella</i>	Designed to detect all subspecies and serovars of <i>Salmonella</i> , including Typhoid and non-Typhoid strains. Susceptibilities will be performed at UMHS and isolates will be sent to the state health department for strain typing. <i>Salmonellosis is a notifiable disease to the health department.</i>	Cross-reactivity may occur with certain <i>E. coli</i> strains containing variants of the cryptic ETT2 type-III secretion system.
<i>Vibrio</i> (<i>V. parahaemolyticus</i> / <i>V. vulnificus</i> / <i>V. cholerae</i>)	Two assays are utilized: The <i>Vibrio</i> assay detects <i>V. parahaemolyticus</i> , <i>V. vulnificus</i> , and <i>V. cholerae</i> ; the second is specific for <i>V. cholerae</i> . If the <i>Vibrio</i> assay result is DETECTED and the <i>Vibrio cholerae</i> assay result is NOT DETECTED, a non-cholera species was detected. A <i>Vibrio cholerae</i> DETECTED result is valid regardless of the <i>Vibrio</i> result. <i>Vibriosis and cholera are notifiable diseases to the health department.</i>	The assay is unable to distinguish between cholera only infection and cholera coinfection with another <i>Vibrio</i> species. The <i>Vibrio</i> assay may react with less common species such as <i>V. alginolyticus</i> , <i>V. fluvialis</i> , and <i>V. mimicus</i> . It does not detect <i>V. cincinnatiensis</i> , <i>V. furnissii</i> , and <i>V. metschnikovii</i> .
<i>Campylobacter</i>	Detects <i>C. jejuni</i> , <i>C. coli</i> and <i>C. upsaliensis</i> . <i>Campylobacter infection is reportable to the health department.</i>	The assay has reduced sensitivity for <i>C. jejuni</i> subspecies <i>doylei</i> . Rare species such as <i>C. lari</i> and <i>C. fetus</i> are not detected.
<i>Yersinia enterocolitica</i>	Single assay for <i>Yersinia enterocolitica</i> . <i>Yersiniosis is a notifiable disease to the health department.</i>	Potential cross-reactivity with <i>Y. kirstensenii</i> and <i>Y. frederiksenii</i> when present at high levels--both organisms are suspected human pathogens.

Parasites

<i>Cryptosporidium</i>	Designed to detect 23 different species, including the two most common species of clinical relevance, <i>C. hominis</i> and <i>C. parvum</i> . <i>Cryptosporidiosis is a notifiable disease to MDCH.</i>	Positive results are not identified on the species level.
<i>Cyclospora cayetanensis</i>	Infections are associated with travelers' diarrhea in persons returning from endemic areas. Outbreaks have been associated with consumption of contaminated food from other countries. <i>Cyclosporiasis is a notifiable disease to the health department.</i>	Detects the only Cyclospora species that is associated with human disease.
<i>Entamoeba histolytica</i>	<i>E. histolytica</i> cysts are generally ingested from materials contaminated with feces, such as food and water, but infection may also be transmitted sexually. Most infections from <i>E. histolytica</i> appear to be asymptomatic but some infections cause invasive amebiasis which results in colitis or dysentery- like illness that can be severe and include amebic liver abscess.	Cross reacts with closely related <i>E. dispar</i> (non-pathogenic) when at high concentrations.
<i>Giardia lamblia</i>	<i>Giardia</i> are the most common intestinal parasites isolated in the US. Populations with the highest risk of <i>G. lamblia</i> infection include children in day care centers, hikers, and the immunocompromised. <i>Giardiasis is a notifiable disease to the health department.</i>	Low frequency cross-reactivity with commensal microbes (Bifidobacterium and Ruminococcus) in clinical evaluation.

Viruses

Astrovirus	Designed to detect all eight subtypes of human Astrovirus (HAastV1-8). It is estimated that there are over 15,000 foodborne illnesses due to Astrovirus in the US each year. The infection route is fecal-oral and at-risk populations include children, immunocompromised adults, caregivers of sick children, military troops, and those in nursing homes.	Does not detect newly-identified Astroviruses of the MLD and VA clades.
Norovirus GI/GII	Detects genogroup (G) I and II that are common in humans. Symptoms of infection generally last 24-48 hours and the illness is self-limiting; though immunocompromised persons may suffer chronic diarrhea and some children have been reported to develop necrotizing colitis.	Norovirus genogroup IV is not detected.

Rotavirus A	Detects all strains of Rotavirus A and will not cross-react with Rotavirus B, C, D, E, or F. Disease rates peak during winter/spring in temperate climates and may account for up to a third of diarrheal diseases presenting to emergency rooms and outpatient clinics during this time in the US	The performance of the FilmArray™ GI Panel has not been established in individuals who received Rotavirus A vaccine.
Sapovirus (Genogroups I, II, IV, and V)	Sapovirus causes disease mostly in children, though adults are susceptible as well, with outbreaks reported in long-term care facilities, prisons, cruise ships, and hospitals in the US. Detects Sapovirus genogroups GI, II, IV, and V.	Sapovirus GIII (a porcine pathogen) is not detected.
Adenovirus F 40/41	Adenovirus F 40/41 are the only known adenovirus types that are GI pathogens and are responsible for 5 to 15% of all acute diarrheal illness in children (especially in those under two years of age). Adults may be infected as well. May be shed in stool for weeks to months after acute illness.	Other species such as Adenovirus B, C, and E that are common respiratory pathogens are not detected.

Target	Detailed Description of Pathogen
<i>Clostridium difficile</i>	Clinical manifestations of <i>C. difficile</i> infection range from asymptomatic carriage (estimated to occur in 3-5% of healthy adults and up to 30% of healthy neonates) to pseudomembranous colitis, involving bloody diarrhea, severe abdominal pain, and fever.
<i>Diarrheagenic E. coli/Shigella</i>	
Enteropathogenic <i>E. coli</i> (EPEC)	Strains may be categorized as typical or atypical depending on the presence of a plasmid encoding bundle-forming pilis (<i>bfpA</i> ; found in typical EPEC). While typical EPEC remains a significant pathogen of young children in the developing world, atypical EPEC is more prevalent in both developing and developed countries. Typical EPEC, however, has been associated with several deadly outbreaks at hospital nurseries in developed countries in the past. Outbreaks appear to peak in the warmer months of summer and early fall. Illness caused by typical EPEC is associated with acute diarrhea whereas atypical EPEC cause a prolonged, non-bloody diarrhea, and vomiting with fever. When untreated in children, EPEC illness can lead to malnutrition and associated growth defects. Asymptomatic carriage of EPEC has also been documented with some studies reporting similar rates to symptomatic individuals.
Enterotoxigenic <i>E. coli</i> (ETEC)	The presence of heat-labile (lt) and/or heat-stable (st) enterotoxins defines Enterotoxigenic <i>E. coli</i> (ETEC). These toxins (which may be found together or separately in ETEC strains) bind to intestinal epithelial cells triggering loss of electrolytes resulting in watery diarrhea. There were 33 documented outbreaks of ETEC in the US between 1975 and 1999. ETEC are transmitted via the fecal-oral route and are becoming more common as a foodborne pathogen. Infected adults may not seek treatment, as infections resolve in a few days with supportive care. ETEC may also be carried asymptotically.
Enterotoxigenic <i>E. coli</i> (EAEC)	Transmission of EAEC is generally by the fecal-oral route via contaminated food and water. EAEC cause an inflammatory diarrheal illness characterized by watery and sometimes bloody stool, accompanied by low grade fever, vomiting, and abdominal pain. EAEC infections may also be asymptomatic. Data regarding the incidence of EAEC are limited due to the lack of widespread testing; however, based upon various studies, EAEC are suggested to be one of the most common causes of diarrheal illness in the US across all age groups, a cause of persistent diarrhea in children and HIV-infected individuals, the second most common cause of travelers' diarrhea, and has been identified as the cause of large outbreaks worldwide.
Shiga-like toxin-producing <i>E. coli</i> (STEC), including <i>E. coli</i> O157.	Shiga-like toxin-producing <i>E. coli</i> (STEC), including <i>E. coli</i> O157 are a primary cause of bloody diarrhea and can progress to a potentially fatal condition known as hemolytic uremic syndrome (HUS; caused by Shiga-like toxin destruction of red blood cells that leads to renal failure), especially in the very young and very old. STEC are important foodborne pathogens. Infections may also be waterborne, transmitted person-to-person, or via contact with animals (especially cattle, which are a reservoir for STEC). Antimicrobial therapy for STEC may lead to an increased risk for HUS, especially in antibiotic-resistant strains, potentially by up-regulating production and thus increasing the amount of Shiga-like toxin available for absorption. A subset of STEC contain the O157 antigen (and flagellar H7 antigen). <i>E. coli</i> O157:H7 is currently the most frequently identified diarrheagenic <i>E. coli</i> in North America.

Shigella/Enteroinvasive <i>E. coli</i> (EIEC)	Shigella/Enteroinvasive <i>E. coli</i> (EIEC). All Shigella are non-motile, gram-negative rods which are typically transferred through person-to-person contact or ingestion of contaminated food or water (humans and other primates are the only known animal reservoirs). Infections are most common where hygiene is compromised, for example institutional settings (day care, nursing homes). Shigella are responsible for multiple illnesses including shigellosis and bacillary dysentery which can result in bloody or non-bloody diarrhea. EIEC is rare in the US and is also less common worldwide than ETEC and EPEC. There are an estimated 130,000 Shigella infections associated with foodborne illness in the US each year; however, no data exists for EIEC.
Bacteria	
<i>Plesiomonas shigelloides</i>	<i>Plesiomonas shigelloides</i> is a gram-negative rod. It is isolated from a wide range of environmental sources including freshwater and many animals, both wild and domestic. Symptoms generally include watery diarrhea, though dysenteric diarrhea can occur, and infections may be prolonged (>2 weeks duration) but are generally self-limiting. Most cases reported in the US are from individuals with pre-existing health problems leading to a more severe disease outcome.
<i>Salmonella</i>	<i>Salmonella</i> may be classified as typhoidal and non-typhoidal based on the disease that they cause. The non-typhoidal <i>Salmonella</i> are associated with intestinal illness resulting in acute, watery diarrhea, often with fever, and are a common cause of foodborne illness in the US and EU. Typhoidal <i>Salmonella</i> cause a severe, systemic disease (typhoid fever) that includes GI illness. Though rare in developed countries, it is common in the developing world (>70% of US cases are related to foreign travel). In contrast, infection with non-typhoidal <i>Salmonella</i> is one of the most common causes of foodborne illness in the US.
<i>Vibrio</i> (<i>V. parahaemolyticus</i> / <i>V. vulnificus</i> / <i>V. cholerae</i>)	Gastrointestinal illness is most commonly associated with <i>V. cholerae</i> , <i>V. parahaemolyticus</i> , <i>V. vulnificus</i> , <i>V. fluvialis</i> , <i>V. mimicus</i> or <i>V. alginolyticus</i> and infections are associated with consumption of contaminated food, particularly in coastal regions. While <i>V. cholerae</i> infections are exceedingly rare in the US, other <i>Vibrio</i> species are estimated to cause approximately 50,000 food-borne infections per year.
<i>Campylobacter</i>	<i>C. jejuni</i> and <i>C. coli</i> are most commonly associated with diarrheal illness followed distantly by <i>C. upsaliensis</i> . <i>C. lari</i> and <i>C. fetus</i> are uncommon. It is the leading cause of bacterial enteritis in the US. The organisms are gram negative, comma-shaped, oxidase and catalase positive. Sporadic ingestion often occurs following ingestion of undercooked poultry. Outbreaks can occur from unpasteurized dairy, contaminated water, poultry and other produce. Transmission from domesticated animals can also occur. The severity of infection ranges from asymptomatic to severe and from non-bloody to bloody diarrhea. It is associated with Guillain-Barre Syndrome and with Reactive Arthritis.
<i>Yersinia enterocolitica</i>	<i>Y. enterocolitica</i> is transmitted through ingestion of contaminated food or water, often raw undercooked meats (especially pork), as well as pet feces, and is estimated to cause almost 100,000 foodborne illnesses in the US annually (though only about 1,000 cases are laboratory-confirmed; possibly because <i>Y. enterocolitica</i> are not identified by routine enteric pathogen testing). The severity of the illness is based on the serotype of the infecting strain and ranges from self-limiting gastroenteritis to terminal ileitis and mesenteric lymphadenitis. Symptoms of illness mimic appendicitis and may lead to unnecessary surgery.
Parasites	

<i>Cryptosporidium</i>	<i>Cryptosporidium</i> is a genus of protozoa capable of causing infections of the human stomach, intestine, and biliary ducts following ingestion of chlorine-tolerant oocysts which are shed in fecal material and can contaminate drinking water, recreational water, or food. <i>Cryptosporidium</i> are among the most common parasitic causes of diarrhea in developed nations. There are an estimated 60,000 illnesses every year in the US due to <i>Cryptosporidium</i> infection with rates being highest in summer months. Severe illness is possible in immunocompromised individuals, particularly those with AIDS, where illness resolves slowly or not at all and can be fatal.
<i>Cyclospora cayetanensis</i>	<i>Cyclospora cayetanensis</i> are parasitic protozoa that cause gastroenteritis in humans, which are the only known hosts. Unsporulated oocysts are disseminated in feces. Infections are most common in tropical, subtropical, or warm temperate regions. There are an estimated 11,000 foodborne illnesses due to <i>C. cayetanensis</i> infections annually in the US. Illness presents as non- bloody diarrhea that may be up to several months in duration.
<i>Entamoeba histolytica</i>	<i>Entamoeba histolytica</i> are pathogenic protozoa which are found worldwide with a particularly high prevalence in tropical and subtropical regions. The epidemiology of <i>E. histolytica</i> is uncertain because it is indistinguishable from non-pathogenic <i>E. dispar</i> using the current clinical reference standard (microscopy). In endemic regions, the prevalence of <i>Entamoeba</i> in stool can be as high as 50% of the general population. An estimated 500 million people world-wide are infected every year with <i>Entamoeba</i> . As <i>E. dispar</i> is thought to be 10-fold more prevalent, this translates to an estimated 50 million <i>E. histolytica</i> infections, which result in more than 100,000 deaths.
<i>Giardia lamblia</i>	Transmission occurs through ingestion of contaminated food or water, with approximately 77,000 foodborne illnesses in the US annually. Infection rates are highest during summer months. The majority of <i>G. lamblia</i> infections are asymptomatic, but those who develop illness experience nausea, fever, and watery diarrhea. Infections are generally self-limiting; though symptoms are long-lasting, and some patients go on to develop chronic illness, which can lead to complications.
Viruses	
Astrovirus	Astroviruses (RNA viruses of the family Astroviridae) are named for their characteristic star-like structure and are found in a variety of animals, including birds and mammals. There are eight serotypes of human Astrovirus (HAstV 1- 8) associated with gastroenteritis in both children and adults. Symptoms are reported to be milder than other enteric viruses and include diarrhea, vomiting, abdominal pain, and fever lasting 72 hours. There is a 70-90% seroprevalence of antibodies to Astrovirus in school-aged children, indicating nearly universal exposure in childhood.
Norovirus GI/GII	Noroviruses are highly contagious members of the Caliciviridae family of RNA viruses and cause moderate to severe gastroenteritis consisting primarily of nausea, vomiting, and diarrhea accompanied by fever. There are five genogroups (GI - GV) of which GI and GII are common in humans and GIV is rare in humans. Transmission occurs via the fecal-oral route or through aerosolized vomitus and the infectious dose may be as low as 18 particles. Outbreaks are common in closed communities such as cruise ships, hospitals, nursing homes, schools, and military installations. Norovirus infections are the leading cause of foodborne gastroenteritis in the US, causing nearly 5.4 million illnesses (and over 14,000 hospitalizations) annually. Peak infection rates occur during winter months.

Rotavirus A.	Rotaviruses are double stranded RNA viruses of the Reoviridae family and are the single most important etiologic agents of severe diarrheal illnesses in infants and young children worldwide. Of the seven groups of Rotaviruses (A through G), Rotavirus A, B, and C infect humans, with Rotavirus A being responsible for the majority of infections. Symptoms of infection may be mild and last for a few days, but prolonged illness can lead to severe dehydration in children <2 years of age and Rotaviruses are shed before and after acute illness and are hardy to environmental factors, allowing them to survive on surfaces and resist inactivation. It is estimated that 2.7 million diarrheal illnesses per year in the US are caused by Rotavirus infection.
Sapovirus (Genogroups I, II, IV, and V)	Five genogroups are present (GI - GV) and all except GIII cause disease in humans. Like Norovirus, Sapovirus is spread via the fecal-oral route and infections are highest during winter months. Symptoms primarily include vomiting and diarrhea with nausea and fever lasting 5 to 10 days. In general, illness is self-limiting with treatment consisting of supportive care. Infections are attributed to an estimated 15,000 foodborne illnesses in the US annually.
Adenovirus F 40/41	Transmission is mostly through fecal-oral spread and outbreaks have been reported in hospitals and child care centers. Illness is generally mild but of a relatively long duration (5-12 days). Immunocompromised patients may suffer chronic, prolonged diarrheal illness and other complications.