Policy Number	**MED207.155**
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Gastrointestinal Panels

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

The use of gastrointestinal panels (CPT 87505 and 87506) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis or infectious colitis **may be considered medically necessary** when the following clinical indications are met:

- Individuals with acute diarrhea with moderate-to-severe symptoms (e.g., fever, bloody or mucoid stools, dysentery, severe dehydration, severe abdominal pain); **OR**
- Individuals with community-acquired diarrhea that persists for more than seven days, or individuals with travel-associated diarrhea of uncertain etiology.

The use of gastrointestinal panels (CPT 87507) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis or infectious colitis **may be considered medically necessary** when the following clinical indication is met:

- Immunocompromised individuals (including but not limited to patients with HIV, patients receiving immunocompromising treatments such as chemotherapy or steroids) with acute diarrhea.

The use of gastrointestinal panels (CPT 87505, 87506, and 87507) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms suggesting a diagnosis of paralytic ileus with persistent abdominal pain lasting 24 hours or less with either fever or nausea and vomiting **may be considered medically necessary**.

The use of gastrointestinal panels to detect and identify bacterial, viral and parasitic nucleic acid in stool samples not meeting the above criteria **is considered not medically necessary**.

The use of gastrointestinal panels to detect gastrointestinal pathogens and associated antibiotic-resistance genes (0369U) **is considered experimental, investigational and/or unproven.**

NOTE 1: Gastrointestinal panel testing is limited to the minimum number of targets needed for decision making.

NOTE 2: When ordering any gastrointestinal panels, the medical record should include a detailed clinical and exposure history as well as a differential diagnosis.

Policy Guidelines

None.

Description

Gastroenteritis is an inflammation of the stomach and the intestines. Symptoms may cause nausea, vomiting and diarrhea. Numerous causes can be attributed to gastroenteritis including infectious organisms (e.g., viruses and bacteria).

According to a 2012 article by the Centers for Disease Control and Prevention (CDC) the number of people who died from gastroenteritis more than doubled from 1999 to 2007. (2) The CDC used information from the National Center for Health Statistics to discover gastroenteritis-associated deaths from among all age groups in the United States. The study noted gastroenteritis associated deaths increased from nearly 7,000 to more than 17,000 per year. Eighty-three percent of deaths were noted in adults over 65 years of age. The most common infectious causes of gastroenteritis-associated deaths were *Clostridium difficile* (*C. difficile*) and norovirus.

Most episodes of acute diarrheal illness due to gastrointestinal (GI) infections are self-limited. A detailed history of the patient's illness along with diagnostic studies can help guide treatment decisions and determine if medication such as antibiotics may be necessary to deal with symptoms.

Prior to the introduction of multiplex nucleic acid amplification tests (NAATs), the evaluation of patients with suspected GI infection necessitated performing bacterial cultures using a series of selective culture media, stains for ova and parasites, enzyme immunoassays, and single-agent polymerase chain reaction (PCR)-based NAATs. (3) Mulitplex NAATs detect DNA or RNA. While NAATs have a high sensitivity for the detection of enteropathogens, and results are available within hours, a positive finding might not indicate infection with a viable organism and microorganisms at nonpathogenic levels may also be detected.

Several commercial gastrointestinal microorganism multiplex nucleic acid-based panels have become available and report decreased turnaround times in identification of pathogens that may be responsible for gastroenteritis. Multiplex NAAT panels vary in the number of specimens that can be tested simultaneously and in turnaround time.

The U.S. Food and Drug Administration (FDA) maintains a list of nucleic acid amplification tests (NAATs) that have been cleared by the Center for Devices and Radiological Health. The indications for use noted on the summary letters for each panel cleared, generally list the specific targets the panel is used to identify.

Regulatory Status
A list of current FDA cleared nucleic acid-based microbial tests is available at: <https://www.fda.gov>.

Table 1. FDA Cleared Nucleic Acid Amplification Tests (NAATs) for Gastrointestinal Panels

NAAT	Manufacturer	FDA 510(k) Number	Product Code
xTAG Gastrointestinal Pathogen Panel (GPP)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	DEN130003, K121454	PCH
PANNAT STEC Test	Micronics, Inc. (Redmond, WA)	K173330	PCH
Progastro SSCS Assay	Gen-Probe Prodesse, Inc (Waukesha, WI)	K123274	PCH
Biocode Gastrointestinal Pathogen Panel	Applied Biocode (Santa Fe Springs, CA)	K180041	PCH
Biocode Pathogen Panel	Applied Biocode (Santa Fe Springs, CA)	K190585	PCH
EntericBio Dx Assay	Serosep, Ltd (Annacotty, IE)	K182703	PCH
Filmarray Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	K140407, K160459	PCH PCH
ProGastro SSCS	Hologic/Genprobe (Waukesha, WA)	K123274	PCH

BD MAX Enteric Bacterial Panel (EBP)	BD Diagnostics (Sparks, MD)	K170308	PCH
Verigene Enteric Pathogen Panel (EP)	Nanosphere, Inc (Northbrook, IL)	K142033, K140083	PCH PCH
xTAG Gastroenterology Pathogen Panel (GPP) Multiplex Nucleic Acid-Based Assay System	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K121894	PCH
FilmArray GI Panel	BioFire Diagnostics, Inc. (Salt Lake City, UT)	K140407	PCH
Great Basin Stool Bacteria Pathogens Panel	Great Basin Scientific, Inc. (Salt Lake City, UT)	K163571	PCH

DEN: de novo; GI: gastrointestinal; FDA: Food and Drug Administration; NAAT: nucleic acid amplification test.

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Several studies of gastrointestinal (GI) pathogen panels have demonstrated overall high sensitivities and specificities and indicated the panels might be useful for detecting causative agents for GI infections, including both foodborne and infectious pathogens. Claas et al. (2013) assessed the performance characteristics of the xTAG Pathogen Panel (GPP; Luminex, Toronto, ON, Canada) compared with traditional diagnostic methods (i.e., culture, microscopy, enzyme immunoassay/direct fluorescent antibody, real-time PCR, or sequencing) using 901 stool samples from multiple sites. (4) The sensitivity of GPP against real-time PCR was >90% for nearly all pathogens tested by real-time PCR; the 1 exception was adenovirus at 20%, but sensitivity could be higher because real-time PCR did not distinguish between adenovirus

species. Kahre et al. (2014) found similar results when they compared the FilmArray GI panel (BioFire Diagnostics, Salt Lake City, UT, USA) with the xTAG GPP. (5) Both panels detected more pathogens than routine testing. Of 230 prospectively collected samples, routine testing identified 1 or more GI pathogens in 19 (8.3%) samples; FilmArray detected 76 (33.0%), and xTAG detected 69 (30.3%). Two of the most commonly detected pathogens in both assays were *C difficile* (12.6% to 13.9% prevalence) and norovirus (5.7% to 13.9% prevalence). Both panels showed >90% sensitivity for the majority of targets.

Using the xTAG GPP, Beckmann et al. (2014) evaluated 296 patients who were either children with gastroenteritis (n=120) or patients who had been to the tropics and had suspected parasite infestation (adults, n=151; children, n=25). (6) Compared with conventional diagnostics, the GPP showed 100% sensitivity for rotavirus, adenovirus, norovirus, *C difficile*, *Salmonella* species, *Cryptosporidium*, and *Giardia lamblia*. Specificity was >90% for all but norovirus (42%) and *G lamblia* (56%); both also had lower positive predictive value (PPV) at 46% and 33%, respectively. *Salmonella* species also had low PPV at 43%; all others had 100% PPV. Negative predictive value (NPV) was 100% for all pathogens.

Buchan et al. (2013) evaluated a multiplex real-time PCR assay (ProGastro SSCS, Gen-Probe Prodesse, SanDiego, CA) limited to *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. against culture; and they tested for STEC against broth enrichment followed by enzyme immunoassay. (7) A total of 1244 specimens from 4 U.S. clinical laboratories were tested. Bidirectional sequencing was used to resolve discrepancies between ProGastro and culture or enzyme immunoassay. The overall prevalence of pathogens detected by culture was 5.6%, whereas the ProGastro assay and bidirectional sequencing showed an overall prevalence of 8.3%. The ProGastro SSCS assay showed a sensitivity of 100% and a specificity of 99.4% to 100% for all pathogens. This is compared with a sensitivity of 52.9% to 76.9% and a specificity of 99.9% to 100% for culture compared with ProGastro SSCS assay.

Al-Talib et al. (2014) assessed the diagnostic accuracy of a pentaplex PCR assay with specific primers to detect hemorrhagic bacteria from stool samples. (8) The primers, which were mixed in a single reaction tube, were designed to detect *Salmonella* spp., *Shigella* spp., enterohemorrhagic *E. coli*, and *Campylobacter* spp., all of which are a particular danger to children in developing countries. The investigators used 223 stool specimens from healthy children and spiked them with hemorrhagic bacteria. All primers designed had 100% sensitivity, specificity, PPV, and NPV.

Jiang et al. (2014) developed a reverse transcription and multiplex real-time PCR assay to identify 5 viruses in a single reaction. (9) The viruses included norovirus genogroups I and II; sapovirus genogroups I, II, IV, and V; human rotavirus A; adenovirus serotypes 40 and 41; and human astrovirus. Compared with monoplex realtime PCR, multiplex real-time PCR assay had sensitivity ranging from 75% to 100%; specificity ranged from 99% to 100%.

The health technology assessment and systematic review by Freeman et al. (2017) evaluated multiplex texts to identify GI pathogens in people suspected of having infectious gastroenteritis.

(10) Tests in the assessment were xTAG® GPP and FilmArray GI Panel. Eligible studies included patients with acute diarrhea, compared multiplex GI pathogen panel tests with standard microbiology tests, and assessed patient, management, and/or test accuracy outcomes. Of the 23 identified studies, none provided an adequate reference standard for comparing the accuracy of GI panels with standard tests, so sensitivity and specificity analyses were not performed. Positive and negative test agreement were analyzed for individual pathogens for the separate panel products and are not detailed in this review. The meta-analysis of 10 studies found high heterogeneity in participants, country of origin, conventional methods used, and pathogens considered. Using conventional methods as the determinant of clinically important disease, the meta-analysis results suggested GI panel testing is reliable and could supplant current microbiological methods. An increase in false positives would result, along with the potential for overdiagnosis and incorrect treatment. However, if GI panel testing is identifying important pathology being missed with conventional methods, the result could be more appropriate treatments. The clinical importance of these findings is unclear, and an assessment of GI panel testing effect on patient management and outcomes, compared with conventional testing, is needed.

Kosai et al. (2021) evaluated the Verigene Pathogens Nucleic Acid Test (Luminex Corporation), testing 268 clinical stool samples for bacteria and toxins and 167 samples for viruses. (11) Of these samples, 256 and 160 samples, respectively, (95.5% and 95.8%) had fully concordant results between the Verigene EP test and the reference methods (which were culture for bacteria and toxins and xTAG GPP for viral detection). Overall sensitivity and specificity were 97.0% and 99.3%, respectively. Sensitivity for individual pathogens ranged from 87.5% to 100%, and specificity ranged from 98.7% to 100%. A total of 13 false-positive and 6 false-negative results were reported.

Ahmed et al. (2024) evaluated the performance of the BioFire FilmArray GI Panel for diagnosing infectious diarrhea caused by parasitic and bacterial infections in intensive care unit patients in Egypt. (12) The study included 50 stool samples subjected to conventional identification (microscopic examination, stool culture, and bacterial identification) and molecular diagnosis by the FilmArray Panel. For parasitic infections, the sensitivity and specificity of the panel compared to microscopy were 83.3% and 100% for *Cryptosporidium* oocysts and 100% and 92.5% for *Giardia lamblia* cysts, respectively. For bacterial infections, the BioFire FilmArray GI Panel demonstrated 100% sensitivity and specificity for both *E. coli* and *Salmonella* compared to stool culture. The overall agreement between the BioFire FilmArray GI Panel and conventional methods was 98% for *Cryptosporidium*, 94% for *G. lamblia*, and 100% for both *E. coli* and *Salmonella*.

Clinically Useful

Meltzer et al. (2022) conducted a single-center RCT investigating antibiotic use in patients with moderate to severe suspected infectious diarrhea presenting to the emergency department. (13) Patients were randomized to receive multiplex PCR testing with the BioFire FilmArray GI panel (n=38) or standard care (usual testing or no testing; n=36). In the PCR arm, subjects received antibiotics in 87% of bacterial or protozoal diarrheal infections (13/15) compared to

46% (6/13) in the control arm (p=.042). No significant differences were found between groups in follow-up symptoms as assessed on days 2, 7, and 30, or emergency department length of stay. The study was terminated early due to the COVID-19 pandemic and thus was underpowered. Additional limitations include potential antibiotic prescribing at subsequent healthcare visits that was not captured and lack of a standardized reference test for the control arm.

Banerjee and Patel (2023) in a review article provided an overview of commercially available genotypic assays that detect individual resistance genes and/or resistance-associated mutations in a variety of specimen types. (14) They discussed how clinical outcomes studies may be used to demonstrate clinical utility of such diagnostics. The authors concluded that advancing development and use of rapid diagnostic tests for identification of antimicrobial resistance (AMR) is a public health and patient care priority. The authors noted that there are currently multiple FDA-cleared genotypic assays that detect individual resistance genes and some mutations from a variety of specimen types. These assays offer hope that rapid resistance detection can lead to more judicious use of antibiotics and reduce emergence and spread of AMR. Robust outcomes studies that demonstrate value of these tests and policies to make them available are needed.

No studies were identified that addressed the use of panels that include both nucleic acid amplification tests (NAATs) to identify an infectious agent and drug susceptibility testing (genotyping) in individuals with GI pathogens.

Chain of Evidence

A 9-month, prospective, multi-center study by Cybulski et al. (2018) assessed the effect of the BioFire FilmArray GI PCR panel on clinical diagnosis and decision-making. It also compared the diagnostic accuracy for patients with positive results obtained exclusively using the GI panel with results obtained using conventional stool culture. (15) Testing on 1887 consecutive fecal samples was performed in parallel using the GI panel and stool culture. The GI panel detected pathogens in significantly more samples than culture; median time from collection to results and collection to initiation of treatment was also significantly less. The use of a GI panel also led to a significant trend toward targeted rather than empirical therapy (r^2=0.65; p=0.009 by linear regression). Results of the GI panels resulted in discontinuation of antimicrobials in 8 of 9 STEC, with just 1 example of GI panel results affecting clinical decision-making. Limitations of the study include the limit to 2 hospitals within a single healthcare system and certain subgroups that were too small for analysis. In addition, it was unclear how the historic controls were used since the current samples were tested with both a GI panel and culture.

The prospective study by Beal et al. (2017) also aimed to assess the clinical impact of the BioFire FilmArray GI panel. (16) Stool samples from 241 patients (180 adults and 61 children) were tested with the GI panel and compared with 594 control patients from the previous year who were tested via culture. The most common pathogens detected by the GI panel were enteropathogenic *E. coli* (n=21), norovirus (n=21), rotavirus (n=15), sapovirus (n=9), and *Salmonella* (n=9). The GI panel patients had significantly fewer subsequent infectious stool tests

compared with the control group. The GI panel patients also had 0.18 imaging studies per patient compared with 0.39 (p=.0002) in the control group. The GI panel group spent fewer days on antibiotic(s) per patient: 1. 73 versus 2.12 in the control group. In addition, average length of time from stool culture collection to discharge was 3.4 days for the GI panel group and 3.9 days for the controls (p=.04). The GI panel improved patient care in several ways: 1) it identified a range of pathogens that might not have been detected by culture, 2) it reduced the need for other diagnostic tests, 3) it resulted in less unnecessary use of antibiotics, and 4) it led to shorter length of hospital stay. Some limitations of the study include not confirming the results in which the GI panel did not agree with standard testing and using a historical cohort as a control group.

UpToDate

UpToDate (2024) addressed Travelers' diarrhea and noted the following for multiplex molecular testing: Multiplex molecular testing is useful for providing rapid results and may allow detection of viral infections such as norovirus, avoiding unnecessary antibiotics. (17) In addition, for chronic diarrhea due to protozoa, molecular testing can be very helpful. Clinical interpretation of molecular test results can be complex, since multiple pathogens may be detected. As an example, in one study including more than 100 patients with travelers' diarrhea, use of a multiplex molecular panel identified multiple pathogens in 76 percent of cases; in contrast, use of conventional stool culture identified a pathogen in 24 percent of cases.

Practice Guidelines and Position Statements

Infectious Diseases Society of America

In the 2017 Infectious Diseases Society of America (IDSA) published clinical practice guidelines for the diagnosis and management of infectious diarrhea. The following recommendations were made: (18):

- In situations where enteric fever or bacteremia is suspected, "culture-independent, including panel-based multiplex molecular diagnostics from stool and blood specimens, and when indicated, culture-dependent diagnostic testing should be performed" (GRADE: strong, moderate).
- In testing for *Clostridioides (Clostridium) difficile* in patients >2 years of age, "a single diarrheal stool specimen is recommended for detection of toxin or toxigenic *C. difficile* strain (e.g., nucleic acid amplification testing)" (GRADE: strong, low).
- NAATs are not recommended for diagnosing CMV.
- It was also noted that "Clinical consideration should be included in the interpretation of results of multiple-pathogen nucleic acid amplification tests because these assays detect DNA and not necessarily viable organisms (GRADE: strong, low).

In 2018, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published weak recommendations with low quality evidence for the use of NAATs to diagnose *Clostridioides (Clostridium) difficile*. (19)

- "The best-performing method (i.e., in use positive and negative predictive value) for detecting patients at increased risk for clinically significant *C. difficile* [CDI] infection" is use

of a "stool toxin test as part of a multistep algorithm ... rather than NAAT along for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission."
- "The most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms" is use of "a NAAT alone or a multistep algorithm for testing ...rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission."

American Academy of Pediatrics

The 32nd edition of the American Academy of Pediatrics (AAP) Red Book (2021) describes the diagnostic and treatment options for many infectious diseases in the pediatric population. (20)

- *Clostridioides (Clostridium) difficile*: NAATs detect genes responsible for the production of toxins A and B, rather than free toxins A and B in the stool, which are detected by EIA. NAAT could be considered alone if a policy in place to screen symptoms; if no policy in place, multi-step algorithms involving EIA, GDH, NAAT plus toxin is recommended.
- Enterovirus: RT-PCR and culture from a variety of specimens.

American College of Gastroenterology

In 2016, the American College of Gastroenterology published clinical guidelines on the diagnosis, treatment, and prevention of acute diarrheal infections in adults. (21)
It recommended, given that "traditional methods of diagnosis (bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection… the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. (Strong recommendation, low level of evidence)."

Centers for Disease Control and Prevention (CDC)

In 2017, the CDC updated its guidelines on norovirus gastroenteritis outbreak management and disease prevention. (22, 23) Real-time reverse transcription-PCR assays, specifically, TaqMan-based realtime assays, which can contain multiple probes, is considered the effective laboratory diagnostic protocol for testing suspected cases of viral gastroenteritis.

National Institutes of Health, et al.

The National Institute of Health (NIH), CDC, and HIV Medicine Association of the Infectious Diseases Society of America (IDSA) published guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. (24) The most recent update took place in 2024. In these guidelines, NAATs are discussed in the following situations:
Clostridioides (Clostridium) difficile:

- Detection of either the *C. difficile* toxin B gene, using NMT, or the *C. difficile* toxin B protein, using an enzyme immunoassay, is required for diagnosis. PCR assays have high sensitivity and can detect asymptomatic carriers.

Additional Summary Information

"One potential drawback of molecular technologies is the need to predefine the particular microbes being sought. In addition, the significance of an identified organism may not be clear as these molecular technologies, which involve nucleic acid amplification, are limited to our existing knowledge of a microbes' genome and do not discriminate between viable and non-viable organisms. As a result, they can detect microbes at nonpathogenic levels. Given the high rates of asymptomatic carriage of enteropathogens, this can be a considerable problem. To confound matters, further multiplex techniques are more commonly associated with increased detection of mixed infections and the relative importance of each pathogen may be unclear." (21)

Summary of Evidence

Gastrointestinal panels are likely to identify a variety of pathogens with high sensitivity, compared with standard methods. One potential drawback, in the use of nucleic acid amplification that has been noted is in the significance of an identified organism may not be clear. The technologies, that involve nucleic acid amplification, do not discriminate between viable and non-viable organisms and as noted previously, multiplex techniques are associated with increased detection of mixed infections and the relative importance of each pathogen may be unclear.

In most cases, where acute diarrhea episodes including traveler's diarrhea are of short duration and self-resolving, laboratory investigation generally is not warranted. However, there may be a subset of patients with an unusual presentation or who are immunocompromised in which access to a rapid method for determining etiologic diagnosis of gastrointestinal infection could lead to valuable early treatment and infection-control processes. In this subset of patients testing for a panel of pathogens may be warranted. Therefore, the use of gastrointestinal panels to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis, infectious colitis, or paralytic ileus may be considered medically necessary when criteria are met.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0369U, 87505, 87506, 87507
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. FDA-Reclassification order- xTAG® Gastrointestinal Pathogen Panel (GPP). DEN130003 (Jan 2013) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
2. Deaths from gastroenteritis double (March 2012- Archived). Centers for Disease control and Prevention. Available at: <https://www.cdc.gov> (accessed October 15, 2024).
3. Yalamanchili H, Dandachi D, Okhuysen PC. Use and Interpretation of Enteropathogen Multiplex Nucleic Acid Amplification Tests in Patients with Suspected Infectious Diarrhea. Gastroenterol Hepatol (NY). Nov 2018; 14(11):646-652. PMID 30538605
4. Claas EC, Burnham CA, Mazzulli T, et al. Performance of the xTAG® gastrointestinal pathogen panel, a multiplex molecular assay for simultaneous detection of bacterial, viral, and parasitic causes of infectious gastroenteritis. J Microbiol Biotechnol. 2013; 23(7):1041-1045. PMID 23711521
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 Microbiol. Oct 2014; 52(10):3667-3673. PMID 25100818
6. Beckmann C, Heininger U, Marti H, et al. Gastrointestinal pathogens detected by multiplex nucleic acid amplification testing in stools of pediatric patients and patients returning from the tropics. Infection. Dec 2014; 42(6):961-970. PMID 25015433
7. Buchan BW, Olson WJ, Pezewski M, et al. Clinical evaluation of a real-time PCR assay for identification of Salmonella, Shigella, Campylobacter (Campylobacter jejuni and C. coli), and shiga toxin-producing Escherichia coli isolates in stool specimens. J Clin Microbiol. Dec 2013; 51(12):4001-4007. PMID24048539
8. Al-Talib H, Latif B, Mohd-Zain Z. Pentaplex PCR assay for detection of hemorrhagic bacteria from stool samples. J Clin Microbial. Sep 2014; 52(9):3244-3249. PMID 24958797
9. Jiang Y, Fang L, Shi X, et al. Simultaneous detection of five enteric viruses associated with gastroenteritis by use of a PCR assay: a single real-time multiplex reaction and its clinical application. J Clin Microbial. Apr 2014; 52(4):1266-1268. PMID 24478418
10. Freeman K, Mistry H, Tsertsvadze A, et al. Multiplex tests to identify gastrointestinal bacteria, viruses and parasites in people with suspected infectious gastroenteritis: a systematic review and economic analysis. Health Technol Assess. Apr 2017; 21(23):1-188. PMID 28619124
11. Kosai K, Suzuki H, Tamai K, et al. Multicenter evaluation of Verigene Enteric Pathogens Nucleic Acid Test for detection of gastrointestinal pathogens. Sci Rep. Feb 04 2021; 11(1): 3033. PMID 33542335
12. Ahmed AO, Abdelaziz AM, Rashed HG, et al. Evaluation of a multiplex polymerase chain reaction for the diagnosis of infectious diarrhea in intensive care unit patients in Upper Egypt. Egypt J lmmunol. Jan 2024; 31(1):1-9. PMID 38224030
13. Meltzer AC, Newton S, Lange J, et al. A randomized control trial of a multiplex gastrointestinal PCR panel versus usual testing to assess antibiotics use for patients with infectious diarrhea in the emergency department. J Am Coll Emerg Physicians Open. Feb 2022; 3(1):e12616. PMID 35072157

14. Banerjee R, Patel R. Molecular diagnostics for genotypic detection of antibiotic resistance: current landscape and future directions. JAC Antimicrob Resist. Feb 17 2023; 5(1):dlad018. PMID 36816746
15. Cybulski RJ, Bateman AC, Bourassa L, et al. Clinical Impact of a Multiplex Gastrointestinal Polymerase Chain Reaction Panel in Patients With Acute Gastroenteritis. Clin Infect Dis. Nov 13 2018; 67(11):1688-1696. PMID 29697761
16. Beal SG, Tremblay EE, Toffel S, et al. A Gastrointestinal PCR Panel Improves Clinical Management and Lowers Health Care Costs. J Clin Microbial. Jan 2018; 56(1). PMID 29093106
17. LaRocque R, Harris JB. Travelers' diarrhea: Epidemiology, microbiology, clinical manifestations, and diagnosis. In: UpToDate, Calderwood SB (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed October 15, 2024).
18. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. Dec 15 2017; 65(12):e45–e80. PMID 29053792
19. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. Mar 19 2018; 66(7):e1-e48. PMID 29462280
20. Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book: 2021 Report on the Committee on Infectious Diseases, 32nd Edition. American Academy of Pediatrics: 2021.
21. Riddle M, DuPont H, Connor B. ACG Clinical guideline: Diagnosis, treatment and prevention of acute diarrheal infections in adults. Am J Gastroenterol. May 2016; 111(5):602-622. PMID 27068718
22. MacCannell T, Umscheil CA, Agarwal RK, et al. Guideline for the Prevention and Control of Norovirus Gastroenteritis Outbreaks in Healthcare Settings. CDC. Updated February 15, 2017. Available at: <https://www.cdc.gov> (accessed May 2, 2024).
23. Hall AJ, Vinje J, Lopman B, et al. Updated Norovirus Outbreak Management and Disease Prevention Guidelines. CDC MMWR. Published March 4, 2011. Available at: <https://www.cdc.gov> (accessed May 2, 2024).
24. NIH Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Updated May 2, 2024. Available at: <https://www.clinicalinfo.hiv.gov> (accessed on May 2, 2024).
25. FDA –Summary ProGastro SSCS Assay K123274 (Jan 2013). Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
26. FDA –Summary FilmArray Gastointestinal (GI) Panel K160459 (Apr 2016). Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
27. CMS-LCD for Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs) (L38229). Centers for Medicare and Medicaid Services – Local Coverage Determination. (Revised: October 16, 2022) Available at: <https://www.cms.gov> (accessed October 15, 2024).
28. FDA-Summary FilmArray GI Panel K140407 (May 2014) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).

29. FDA-Summary Biocode Gastrointestinal Pathogen Panel (GPP) K190585. (Jun 2019) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
30. FDA-Summary EntericBio Dx Assay. K182703 (Jun 2019) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
31. FDA-Summary BD Max Extended Enteric Bacterial Panel, BD Max System K170308 (May 2017) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
32. FDA-Summary Verigene® Enteric Pathogens Nucleic Acid Test (EP) K142033 (Oct 2014) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
33. FDA-Summary Verigene® Enteric Pathogens Nucleic Acid Test (EP) K140083 (Jun 2014) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).
34. FDA-Summary xTAG® Gastrointestinal Pathogen Panel (GPP) K121894 (Mar 2013) Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed October 15, 2024).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2024	Document updated with literature review. Coverage unchanged. References 8, 9, 12, 15, 16, 19, 20, 22-24 added; others updated; some removed.
01/01/2024	Document updated with literature review. The following change was made to Coverage: Added “The use of gastrointestinal panels to detect gastrointestinal pathogens and associated antibiotic-resistance genes (0369U) is considered experimental, investigational and/or unproven”. Added references 4, 7-11, 26, others updated, some removed.
05/01/2023	Document updated with literature review. Coverage unchanged. Reference 8 was added, other references were updated, and one reference was removed.
12/01/2022	Reviewed. No changes.

11/01/2021	Document updated with literature review. The following change was made to Coverage: Clarified the following statement to "The use of gastrointestinal panels (CPT 87505, 87506, 87507 and 0097U) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms suggesting a diagnosis of paralytic ileus with persistent abdominal pain lasting 24 hours or less with either fever or nausea and vomiting may be considered medically necessary". References 3, 8, and 14-20 added; one reference removed.
05/01/2020	Document updated with literature review. The following change was made to Coverage: Added "The use of gastrointestinal panels (CPT 87505, 87506, 87507 and 0097U) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of suggesting a diagnosis of paralytic ileus with either persistent abdominal pain with fever or nausea and vomiting lasting 24 hours or less may be considered medically necessary." Reference 13 added.
03/15/2020	Document updated with literature review. Coverage has changed from experimental, investigational and/or unproven to: The use of gastrointestinal panels (CPT 87505 and 87506) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis or infectious colitis may be considered medically necessary when the following clinical indications are met: Individuals with acute diarrhea with moderate-to-severe symptoms (e.g. fever, bloody or mucoid stools, dysentery, severe dehydration, severe abdominal pain); OR Individuals with community-acquired diarrhea that persists for more than seven days, or individuals with travel-associated diarrhea of uncertain etiology. The use of gastrointestinal panels (CPT 87507 and 0097U) to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis or infectious colitis may be considered medically necessary when the following clinical indications are met: Immunocompromised individuals (including but not limited to patients with HIV, patients receiving immunocompromised treatments such as chemotherapy or steroids) with acute diarrhea. The use of gastrointestinal panels to detect and identify bacterial, viral and parasitic nucleic acid in stool samples not meeting the above criteria is considered not medically necessary. Notes 1 and 2 were added. Reference 12 added.
10/01/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. Coverage unchanged.
10/01/2016	Reviewed. No changes.
01/01/2015	New medical document. The use of gastrointestinal panels to detect and identify bacterial, viral and parasitic nucleic acid in stool samples from individuals with signs and symptoms of gastroenteritis or infectious colitis is considered experimental, investigational and/or unproven, including but not

	limited to xTAG® Gastrointestinal Pathogen Panel (GPP), ProGastro SSCS assay and FilmArray® Gastrointestinal (GI) Panels.