Anthem

Clinical UM Guideline

Subject: Molecular Gastrointestinal Pathogen Panel (GIPP) Testing for Infectious Diarrhea in the Outpatient Setting
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Description

Diarrhea and other gastrointestinal infections may be caused by a variety of bacteria, parasites, protozoa, and viruses. Traditional diagnosis of these infections frequently involves culture and microscopy procedures which are time-consuming and lack sensitivity. Newer diagnostic testing methods employ single pathogen tests and multiplex molecular assays (panels) that allow for the rapid detection and identification of gastrointestinal pathogens using a single stool sample.

This document addresses the use of culture-independent single pathogen and panel diagnostic techniques that use polymerase chain reaction (PCR) or real-time PCR and reverse-transcription PCR to amplify targets and detect the ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) of potential gastrointestinal pathogens, in the outpatient setting (Amjad, 2020).

Clinical Indications

Medically Necessary:

1. Multiplex PCR-based panel testing of gastrointestinal pathogens using limited panels involving 5 targets or less is considered **medically necessary** for the following indications:
   A. Individuals suspected of having community-acquired diarrhea of ≥ 7 days duration;**or**
   B. Individuals suspected of having travel-associated diarrhea of uncertain etiology;**or**
   C. Individuals with signs, symptoms or risk factors for severe disease including but not limited to fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain, or an immunocompromised state.
2. Multiplex PCR-based panel testing of gastrointestinal pathogens using large panels involving 6 or more targets is considered **medically necessary** for individuals with diarrhea who are immunocompromised when the clinical scenario presents with overlapping symptoms consistent with multiple possible microbiological etiologies.

Not Medically Necessary:

1. Multiplex PCR-based panel testing of gastrointestinal pathogens is considered**not medically necessary** in individuals not meeting the medically necessary criteria above.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Limited panels
When services may be Medically Necessary when criteria are met:

CPT

87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets

ICD-10 Diagnosis

All diagnoses

Large panels
When services may be Medically Necessary when criteria are met:

CPT

87506	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets
87507	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets [for example, xTAG®]

ICD-10 Diagnosis

All diagnoses

When services are Not Medically Necessary:
For the procedure codes listed above when medical necessity criteria are not met.

Discussion/General Information

Diarrhea and other gastrointestinal infections (GI) may be caused by a variety of bacteria, parasites, protozoa, and viruses. Although

most cases of diarrhea and GI infections are self-limiting, they can be severe and even fatal in immunocompromised individuals, young children, and the elderly. Traditional diagnosis of these infections is typically performed using culture, microscopy, and antigen detection immunoassays. However, traditional culture and microscopy procedures are time-consuming, lack sensitivity, and require special laboratory setup and well-trained staff.

More recently, researchers have been exploring the use of molecular tests that detect multiple pathogens associated with an infectious syndrome rather than a single organism. Molecular technologies with multiplexing capabilities may employ PCR or real-time PCR and reverse-transcription PCR to amplify targets. These molecular tests are typically offered as a panel that simultaneously identifies the pathogens most commonly associated with a particular infectious syndrome, such as sepsis, urinary tract, respiratory, or GI infections, using a single specimen.

Sensitivity, Specificity, and Predictive Value

Several commercially available gastrointestinal pathogen panels are currently available. Because the various panels test for a variety of combination of pathogens, the rate of sensitivity, specificity and predictive value will vary from one test to another and depending on the target being detected. Overall, the sensitivity, specificity and predictive value of the gastrointestinal panel tests are relatively high.

The xTAG® Gastrointestinal Pathogen Panel (GPP) (Luminex Molecular Diagnostics, Inc., Austin, TX) is a qualitative, multiplexed in vitro diagnostic test intended to simultaneously detect and identify microorganism nucleic acids from human stool samples. xTAG is capable of identifying 19 GI pathogens in 6 hours, using a single stool specimen. The Food and Drug Administration (FDA) 510(k) Substantial Equivalence Determination Decision Summary for the XTAG GPP reported the overall sensitivity of xTAG GPP to be 80.0%-100.0% for all analytes with the exception of Enterotoxigenic E. coli (ETEC). The sensitivity for ETEC was reported to be 25.0% (2/8). The specificity of the xTAG GPP assay spanned from 89.8%-99.9%, with a negative predictive value of > 99%. In spite of this relatively high level of specificity, the US-FDA issued a “presumptive positive” warning on the xTAG GPP assay requiring confirmation of positive results by another FDA approved method. The sensitivity for Salmonella was reported with 100% sensitivity (10/10) and 98.4% specificity (1143/1161) (FDA[b]).

In 2014, Beckmann and colleagues reported the findings of a study that evaluated the xTAG GPP in identifying GI pathogens in individuals returning from the tropics. The study included a total of 312 participants: 127 pediatric subjects with gastroenteritis and 185 adult travelers with suspected parasitic infections. Multiplex xTAG GPP was evaluated against a combination of comparator methods: bacterial culture, microscopy and direct antigen detection. Compared with conventional diagnostics, xTAG GPP demonstrated 100% sensitivity for adenovirus, C. difficile, norovirus, rotavirus, Salmonella species, Cryptosporidium, and Giardia lamblia. Specificity was > 90% for all with the exception of norovirus (42%) and G. lamblia (56%), which both also had lower positive predictive value (PPV) at 46% and 33%, respectively. Salmonella species demonstrated a low PPV at 43%; all other pathogens had 100% PPV. Negative predictive value was 100% for all pathogens.

Claas and associates (2013) reported on the performance of the xTAG GPP in detecting bacterial, viral, and parasitic causes of infectious gastroenteritis. With regards to the identification of norovirus (both norovirus GI and GII), the authors found xTAG GPP is comparable to real-time PCR, with a 100% sensitivity and specificity for norovirus GI and 92.5% sensitivity and 97.6% for norovirus GII. Giardia was reported to be identified with 100% sensitivity and 98.9% specificity when using real-time PCR as comparator. The positive agreement for adenovirus 40/41 was 20% (4/20) when compared to real-time PCR but 100% (9/9) when compared to bidirectional sequencing.

Similar to the xTAG GPP, the FilmArray® GI Panel (BioFire, Salt Lake City, UT) is a quantitative, multiplex assay capable of the simultaneous detection and identification of nucleic acids from 22 of the most common pathogens of infectious diarrhea directly from single stool sample in 1 hour. According to the 510(k) Substantial Equivalence Determination Decision Summary, the sensitivity of the FilmArray GI Panel ranged from 94.5%-100% and the specificity ranged from 97.1%-100%, depending on the pathogen being tested. The overall assay success rate for samples in the trial was 99.4% for the initial testing and 99.9% upon repeat testing (FDA[a]).

Buss and colleagues (2015) conducted a cross-sectional trial to assess the clinical validity of the FilmArray GI Panel and standard bacterial culture testing. Prospectively collected stool specimens (n=1556) were evaluated using the BioFire FilmArray GI Panel and compared with conventional stool culture and molecular testing. The majority of the specimens (86.8%) were collected from subjects treated on an outpatient basis, while hospitalized and emergency room subjects represented by 10.5% and 2.7% of the total study population, respectively. Cultures were set up within 4 days following specimen collection. FilmArray was conducted by blinded BioFire personnel for comparator testing. With respect to standard methods of detection, the authors found that FilmArray is associated with sensitivities ranging from 94.5% to 100% and specificities ranging from 97.1% to 100% across pathogen types. Limitations of this study include but are not limited to the fact that all study specimens were originally submitted to the clinical centers based on a healthcare provider’s request for stool culture, not necessarily for parasitic or viral pathogen testing. Thus, prevalence might be influenced to favor organisms detected by traditional stool culture. Another limitation of the study includes the low numbers of positive specimens obtained for some FilmArray GI Panel targets, for example, E. histolytica, Vibrio spp., V. cholerae, and Y. enterocolitica. The sensitivities for these four pathogens could not be evaluated at all (or with confidence for Y. enterocolitica) due to their low prevalence during the study.

Clinical Utility

The study by Kahlau (2013) demonstrated that the xTAG GPP assay provided same day results while conventional methods took about 3 days. Multiplex assays also gave 19 (of 104 total) positive results that were not requested by ordering physicians (Kahlau, 2013).

Cybulski and colleagues (2018) conducted a prospective, multi-center trial to assess the impact of the BioFire FilmArray GI panel on clinical diagnosis and decision-making. A total of 1887 consecutive fecal specimens were analyzed in parallel using the FilmArray panel test and stool culture. Laboratory and medical records were examined to determine detection rates, turnaround times, clinical features, and the nature and timing of clinical decisions. FilmArray identified pathogens in 35.3% of specimens, versus 6.0% for culture. Median time from collection to test results was 18 hours for FilmArray and 47 hours for culture. Median time from specimen collection to initiation of antimicrobial therapy was 22 hours for FilmArray and 72 hours for culture. The FilmArray panel resulted in a significant trend toward targeted rather than empirical therapy, compared to those diagnosed by culture (p=0.0148). Positive Shiga-like toxin-producing E. coli results were reported 47 hours sooner with FilmArray and facilitated discontinuation of empirical antimicrobials. Participants diagnosed exclusively by FilmArray had clinical characteristics similar to those identified by culture. Limitations of the study include the use of only two hospitals within a single healthcare organization although the county hospital, academic medical center, and the 17 community clinics they support collectively represent an extensive metropolitan demographic that includes both healthy immunocompetent individuals and subjects with various forms of immunocompromise and chronic illness. Another limitation of the study was the insufficient size of certain subgroups to draw definitive conclusions regarding small observed differences.

In 2018, Beal and colleagues reported the results of a study that examined the clinical impact of the BioFire FilmArray GI panel. Stool

samples from a total of 241 participants (180 adults and 61 children) were tested with the GI panel and compared with 594 control subjects from the previous year who were tested via culture. The most common organisms identified by the FilmArray GI panel were enteropathogenic Escherichia coli (EPEC, n=21), norovirus (n =21), rotavirus (n=15), sapovirus (n=9), and Salmonella (n=8). Participants tested using the GI panel had an average of 0.58 other infectious stool tests compared with 3.02 in the control group (p=0.0001). The number of days on antibiotic(s) per participant were 1.73 in the cases and 2.12 in the controls (p=0.06). Subjects tested with the GI panel had 0.18 abdomen and/or pelvic imaging studies per subject compared with 0.39 (p=0.0002) in the controls. The average length of time from stool culture collection to discharge was 3.4 days in the FilmArray GI panel group versus 3.9 days in the controls (p=0.04). The BioFire FilmArray GI panel positively impacted subject care by rapidly identifying a broad range of pathogens which may not have otherwise been detected, reducing the need for other diagnostic tests, reducing the use of unnecessary antibiotics, and leading to a reduction in hospital length of stay. Some limitations of the study include use of a historical cohort as a control group and not confirming the results in which the GI panel did not agree with standard testing.

Cotter and colleagues carried out a multicenter, cross-sectional study to assess the clinical impact of GI panel (GIP) testing in children who underwent stool testing from 2013 to 2017. Researchers utilized bivariate analyses to compare test use, results, and participant outcomes, including length of stay (LOS), ancillary testing, and hospital charges, between the GIP era (24 months after GIP introduction) and conventional diagnostic era (historic control, 24 months before). There was a total of 12,222 tests performed in 8720 encounters. In the GIP era, there was a 21% increase in the proportion of participants who underwent stool testing, with a statistically higher percentage of positive results (40% vs 11%), decreased time to result (4 vs 31 hours), and decreased time to treatment (11 vs 35 hours). While there was a decrease in LOS by 2 days among the participants who received treatment of a bacterial and/or parasitic pathogen (5.1 vs 3.1; p<0.001), this represented only 3% of tested children. In the overall population, researchers found no statistical difference in LOS, ancillary testing, or charges. The authors concluded that the GI panel resulted in faster results and increased pathogen detection which resulted in improved outcomes for only a small subset of participants. The authors also cautioned against using the GI panel in an unrestricted manner and acknowledged that limiting the study to 4 facilities within a single health care system limits the generalizability of the test results to the general population (Cotter, 2021).

Professional/Medical Society Recommendations

Both the Infectious Disease Society of American (IDSA) and the American College of Gastroenterology ACG) have published clinical guidelines addressing the use of GPPs.

The Infectious Diseases Society of America guidelines on the Diagnosis and Management of Infectious Diarrhea (Shane, 2017) include the following recommendations:

- 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 (strong, low).
- A broad differential diagnosis is recommended in immunocompromised people with diarrhea, especially those with moderate and severe primary or secondary immune deficiencies, for evaluation of stool specimens by culture, viral studies, and examination for parasites (strong, moderate). People with acquired immune deficiency syndrome (AIDS) with persistent diarrhea should undergo additional testing for other organisms including, but not limited to, Cryptosporidium, Cyclospora, Cystoisospora, microsporidia, Mycobacterium avium complex, and cytomegalovirus (strong, moderate).
- Diagnostic testing is not recommended in most cases of uncomplicated traveler's diarrhea unless treatment is indicated. Travelers with diarrhea lasting 14 days or longer should be evaluated for intestinal parasitic infections (strong, moderate). Testing for C. difficile should be performed in travelers treated with antimicrobial agent(s) within the preceding 8-12 weeks. In addition, gastrointestinal tract disease including inflammatory bowel disease (IBD) and postinfectious irritable bowel syndrome (IBS) should be considered for evaluation (strong, moderate).
- 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 (strong, low).
- All specimens that test positive for bacterial pathogens by culture-independent diagnostic testing such as antigen-based molecular assays (gastrointestinal tract panels), and for which isolate submission is requested or required under public health reporting rules, should be cultured in the clinical laboratory or at a public health laboratory to ensure that outbreaks of similar organisms are detected and investigated (strong, low). Also, a culture may be required in situations where antimicrobial susceptibility testing results would affect care or public health responses (strong, low).
- Culture-independent, including panel-based multiplex molecular diagnostics from stool and blood specimens, and, when indicated, culture-dependent diagnostic testing should be performed when there is a clinical suspicion of enteric fever (diarrhea uncommon) or diarrhea with bacteremia (strong, moderate). Additionally, cultures of bone marrow (particularly valuable if antimicrobial agents have been administered), stool, duodenal fluid, and urine may be beneficial to detect enteric fever (weak, moderate). Serologic tests should not be used to diagnose enteric fever (strong, moderate).

The American College of Gastroenterology Clinical Guideline on acute diarrheal infections in adults (Riddle, 2016) provides a discussion of the benefits and limitations of GI pathogen panels. According to the ACG:

- Diarrheal disease by definition has a broad range of potential pathogens particularly well suited for multiplex molecular testing. Several well-designed studies show that molecular testing now surpasses all other approaches for the routine diagnosis of diarrhea. Molecular diagnostic tests can provide a more comprehensive assessment of disease etiology by increasing the diagnostic yield compared with conventional diagnostic tests). They are also faster, providing results in hours rather than days). The new diagnostics' best applicability is for the clinician in practice, seeing one participant at a time rather than in the public health setting, e.g., in outbreak investigations. 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.
- Before bacterial culture is discarded entirely, it is important to acknowledge that multiplex molecular diagnostics do not yield isolates that can be forwarded to public health laboratories. Specimens collected for culture-independent testing may, in some cases, be incompatible with culture because of the collection methods or media that are used for collection. And, a strict reliance on culture-independent diagnostics would limit our ability to detect new causes of diarrheal disease.
- Conventional diagnostic approaches to diarrheal disease require multiple procedures: bacterial culture, microscopy with and without stains or immunofluorescence and stool antigen tests for detection of protozoa, and for detecting viral agents, electron microscopy, or antigen-based tests. Routine clinical laboratory detection of bacterial pathogens requires the use of differential culture media, which select for the growth of certain bacteria but may fail to detect other bacteria, especially in the setting of antibiotic use. Culture methods are laborious and time consuming, with results often not available for 48 to 72 h. Historically, a decision to obtain a stool culture in an individual with diarrhea has often been guided by the finding of fecal leukocytes or the presence of stool lactoferrin. Although the latter is a more sensitive predictor of a positive stool culture, using these markers to

guide further diagnostic studies has been proven to be imprecise and probably unnecessary.

- Stool diagnostic studies may be used if available in cases of dysentery, moderate-to-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. (Strong recommendation, very low level of evidence).
- 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. If available, the use of Food and Drug Administration-approved culture independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. (Strong recommendation, low level of evidence).
- Molecular diagnostic tests can provide a more comprehensive assessment of disease etiology by increasing the diagnostic yield compared with conventional diagnostic tests. They are also faster, providing results in hours rather than days. The new diagnostics' best applicability is for the clinician in practice, seeing one patient at a time rather than in the public health setting, e.g., in outbreak investigations. 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.

Summary

The use of GIP panels to identify the cause of gastrointestinal disorders continues to evolve. The peer-reviewed literature evaluating the sensitivity and specificity of GIP panel testing in individuals who have signs and/or symptoms of a GI infection consists largely of prospective and retrospective studies. Trials examining the clinical utility of GIP panel testing in individuals suspected of having a GI infection consist of prospective studies. Research suggests that when compared to standard testing methods, GIP panel tests are likely to identify both bacterial and viral pathogens with a high degree of sensitivity and specificity, but the yield of testing may be affected by the panel composition. At least two studies (Beal 2018; Cylbuski 2018) demonstrated the GIP panel test resulted in quicker turnaround times, facilitated more prompt treatment and influenced patient management by directing treatment away from empirical treatment toward targeted therapy. Overall, the use of GIP panels to identify individuals with a GI infection may lead to more effective early treatment and infection-control measures, however, in those instances when the cause of the GI infection is believed to be caused by a single pathogen, an individual pathogen test or a limited GIP panel test may be appropriate.

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Government Agency, Medical Society, and Other Authoritative Publications:

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Websites for Additional Information

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated review date, References, Websites for Additional Information and History sections. Updated Coding section to remove 0369U now addressed in LAB.00039; also removed diagnosis examples.
	12/06/2023	Revised References section.
Reviewed	02/16/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated review date, References, Websites for Additional Information and History sections. Updated Coding section with 04/01/2023 CPT changes; added 0369U.
Reviewed	02/17/2022	MPTAC review. Updated review date, References, Websites for Additional Information, Index and History sections. Updated Coding section, removed CPT code 0097U deleted 03/31/2022.
New	02/11/2021	MPTAC review. Initial document development.
