Medicare Local Coverage Determination Policy

Multiplex Gastrointestinal Pathogen Panel (GPP) Tests for Acute Gastroenteritis (AGE)

CPT: 87506 AND 87507

CMS Policy for Illinois, Minnesota, and Wisconsin

Local policies are determined by the performing test location. This is determined by the state in which your performing laboratory resides and where your testing is commonly performed.

Medically Supportive ICD Codes are listed on subsequent page(s) of this document.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity
Indications and Limitations of Coverage*

One† multiplex GPP^ is covered when at least **ONE** of the following applies:

1. Community-acquired acute diarrhea (≥3 loose or watery stools/day for ≤14 days) with at least **ONE** of the following (1-3):
    1. >1 week duration
    2. Severe illness (e.g., profuse watery diarrhea, signs of hypovolemia, passage of ≥6 unformed stools per 24 hours, severe abdominal pain, need for hospitalization)
    3. Inflammatory diarrhea (bloody diarrhea, small volume mucous stools, fever)
    4. High-risk host (e.g., age ≥70 years, cardiac disease, immunocompromising condition, inflammatory bowel disease, pregnancy)
    5. Public health concerns (e.g., food handler, health care or day care worker)

2. Pre-transplant evaluation (4)

Contraindications to Coverage (ANY)

1. As a test of cure (3,5)

2. More than 72 hr. after hospitalization while still an inpatient (1,6-8)

3. Laxatives in the prior 48 hours (7, 32), excluding those with signs of severe disease

*See associated Billing & Coding article for specific diagnosis codes, POS, and credentialing requirements.

†A second panel test for the same clinical indication is covered if the first panel yielded a negative result AND there is a high index of suspicion for a pathogen as the cause of symptoms, AND the patient's clinical condition is not improving or is deteriorating, AND as long as the test fulfills the criteria for coverage set forth in the LCD.

^Tests must be FDA approved/cleared, or if a laboratory developed test (LDT), have a published, peer-reviewed study supporting analytic validity, or certification by a third-party consistent with the New York State Department of Health's Clinical Laboratory Evaluation Program (CLEP) review standards.

Summary of Evidence

The CDC estimates nearly 48 million AGE US cases annually, costing approximately $150M (3). A wide spectrum of responsible enteric pathogens include bacteria (e.g., campylobacter, clostridium difficile, salmonella, shigella, vibrio, yersinia); viruses (e.g., norovirus, rotavirus, astrovirus, adenovirus); and parasites (e.g., giardia, entamoeba histolytica and cryptosporidium) (3,9). AGE cases are usually self-limited with no laboratory testing recommended (10) except for certain populations such as immunocompromised hosts, the critically ill, and those with prolonged disease refractory to treatment. Sequelae can include Guillain-Barré syndrome, reactive arthritis, irritable bowel syndrome, malabsorption syndrome, or hemolytic uremic syndrome (11). Therefore, in select cases, expeditious pathogen identification is important to facilitate appropriate therapy, local infection control, and epidemiologic measures.

Traditionally, diarrheal pathogens have been identified using cultures for bacteria, monoplex (one-target) polymerase chain reaction (PCR) assays for viruses, and microscopy or enzyme immunoassays (EIA) for parasites. However, such methods are time-consuming, labor-intensive, operator-dependent, and often involve test selection based on clinically indistinguishable illness (12). Turn-around times of several days is typical, during which a patient is isolated with empiric or no therapy (13). Recently, multiplex GPPs, which exploit multiplex nucleic acid amplification methodology, have gained traction due to reduced sample volume requirements, broad coverage without the need to select specific tests, enhanced ability to detect coinfections, increased sensitivity, higher throughput, and faster turnaround time to ≤ 1 day (9,12).

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Three longstanding FDA-approved/cleared multiplex GPP assays that detect >5 stool pathogens are the Luminex xTAG gastrointestinal pathogen panel (Luminex GPP; Luminex Corporation, FDA approval/clearance 2013, 14 targets), the BioFire FilmArray gastrointestinal panel (BioFire GIP; BioFire Diagnostics, FDA approval/clearance 2014, 22 targets), and the Verigene Enteric Pathogens panel (Verigene EP, Luminex Corporation, FDA approval/clearance 2014, 9 targets) (14). A substantial body of research evaluating the BioFire GIP and Luminex GPP is available and demonstrates that both assays yield more positive results (22-74%) than conventional testing (8-18%) methods (15-17), likely due to a combination of greater sensitivity and target number. The most commonly detected organisms are C. difficile, enteropathogenic E. coli (EPEC), enteroaggregative E. coli (EAEC), salmonella, norovirus, rotavirus, sapovirus, and cryptosporidium (15-19). One study comparing GPPs to conventional testing in 152 stool from patients with ACE found the range of sensitivity/specificity to different pathogens common to each was BioFire (94.7-100%/98.6-100%), Luminex (79.2-100%/100%), Verigene (71.4-95.4%/99.1-100%) (20). All three GPPs detected the majority of gastrointestinal pathogens when compared to conventional methods.

Multiplex GPPs consistently detect multiple targets more frequently than conventional testing. One study of 709 samples found multiple pathogens in 16.4% of samples using the BioFire GIP versus 1% after conventional testing (17). Among samples with multiple pathogens, 84% were positive for EAEC or EPEC. Impact studies have found that GPP testing is associated with a significant decrease in endoscopic procedures, abdominal imaging, antibiotic use, and reduced hospital length of stay (7,11,21). A prospective multi-center study evaluating 1887 fecal specimens from patients with AGE found that use of a GI panel enhanced organism detection and improved clinical sensitivity, and enabled clinicians to provide more timely and targeted antimicrobial therapy (22). Positive Shiga-like toxin producing E. coli (STEC) results led to appropriate discontinuation of empiric antibiotics sooner. A study in patients with inflammatory bowel disease (IBD) found that GPP testing led to lower rate of IBD treatment modification (23). In outpatients with IBD relapse, testing was associated with significantly lower rates of IBD therapy escalation and endoscopy compared to patients who underwent conventional testing (24). A study evaluating GI infections prior to hematopoietic cell transplantation (HCT) in 112 asymptomatic patients found more than one-third were colonized with a wide range of GI pathogens, with colonization predicting the infectious etiology of post-transplantation diarrhea in nearly 75% of cases (4). The authors suggest that pre-transplant GPP testing may be warranted in asymptomatic patients.

A systematic review and meta-analysis of 10 studies compared GPP tests with standard microbiology techniques in patients with suspected AGE (25). The authors determined that no study provided an adequate reference standard with which to compare the test accuracy of GPP and conventional tests. In the absence of a reference standard, test performance was analyzed taking GPP tests and standard microbiology techniques in turn as the benchmark test, using random effects meta-analysis of proportions. Positive agreement across all pathogens was 0.93 (95% CI 0.90 to 0.96) when conventional methods were the benchmark and 0.68 (95% CI: 0.58 to 0.77) when GPP provided the benchmark. Negative agreement was high in both instances due to the high proportion of negative cases. The authors conclude: “GPP testing has the potential to simplify testing and accelerate reporting when compared to conventional microbiology methods. However the impact of GPP testing upon the management, treatment and outcome of patients is poorly understood and further studies are needed to evaluate the health economic impact of GPP testing compared with standard methods….GPP testing produced a greater number of pathogen-positive findings than conventional testing. It is unclear whether these additional 'positives' are clinically important.”

Another systematic review and meta-analysis included 11 studies with 7085 stool samples (12). Multiplex PCRs demonstrated high diagnostic accuracy, with specificity ≥0.98 and area under the ROC curve (AUROC) ≥0.97 for all the pathogens except for Yersinia enterocolitica (AUROC 0.91). The Biofire GIP demonstrated a higher sensitivity than Luminex xTAG GPP for most of the pathogens with the exception of Rotavirus A (xTAG GPP and Biofire GIP were both 0.93). They conclude that “both GI panels are highly accurate and may provide important diagnostic information for early identification of gastroenteritis.”

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While apparent superiority of fundamentals such as sensitivity and specificity are important, findings can be challenging to interpret when there is no clear "gold standard". "Pathogens detected may represent colonization, asymptomatic infection, reactivation in the setting of acute infection, chromosomal integration, or prolonged shedding after an unrelated prior infection" (26). Detection of nucleic acids does not necessarily equate to detection of a viable organism responsible for the patient's disease. Interpretation complexity is exacerbated by inappropriate use; a retrospective, observational, cohort study of 442 BioFire GIP tests found that 61% were deemed inappropriately ordered (7). Primary reasons were lack of documented diarrhea (n = 92), greater than 2 days of hospitalization (n = 116), having a duplicate C. difficile PCR test ordered (n = 118), or laxative use in the 48 hours before testing (n = 36). Another study of 481 BioFire GIP tests found a low diagnostic yield (3%) in adult patients hospitalized for >72 hours (6). Careful diagnostic and antimicrobial stewardship is essential for responsible GPP implementation (6-8,14,26).

Analysis of Evidence (Rationale for Determination) Studies show multiplex GPP testing produces a greater number of pathogen-positive findings than conventional testing, with overall high sensitivity and specificity. This led to a paradigm shift in AGE diagnosis, providing a single test to detect a number of organisms associated with an infectious syndrome rather than a series of individual, pathogen-specific assays (14). Reducing turnaround time from days to hours facilitates earlier, specific (non-empiric) antibiotic treatment.

Guidelines from the American College of Gastroenterology (ACG) regarding acute diarrheal infections in adults are supportive of multiplex GPPs as a potential alternative to traditional tests (3).

1. 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).

2. Historical guidelines for diagnostic testing (ACG, IDSA) seem to be too restrictive in the current environment of new diagnostic methods and enhanced ability to target therapy.

3. 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 FDA-approved culture independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. (Strong recommendation, low level of evidence).

4. 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.

5. 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.

Guidelines from the Infectious Diseases Society of America (ISDA) are also generally supportive of multiplex GPPs with some caveats (5).

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1. Stool culture often fails to detect the causative agent and, when necessary, culture-independent methods are recommended as adjunct methods.

2. Selective use of multiplex nucleic acid amplification tests (NAATs) for stool pathogens is very sensitive and, when positive for reportable agents, should either be cultured to recover the isolate or the stool provided to public health laboratories to culture, for epidemiologic follow-up.

3. Culture independent methods can detect pathogens in as little as 1–5 hours compared to the 24–96 hours often required for culture. These assays are reported to be more sensitive than culture and have resulted in much higher rates of detection.

4. Highly multiplexed assays allow for the detection of mixed infections, where the importance of each pathogen is unclear, and they may allow for the detection of pathogens, such as enteroaggregative E. coli or sapovirus, where the indication for therapy is unclear.

5. Culture-independent methods should not be used as test of cure as they will detect both viable and nonviable organisms.

Other analyses remain guarded. A 2017 National Institute for Health and Care Excellence (NICE) guideline (27), based on a Health Technology Assessment (28), is circumspect: “There is currently insufficient evidence to recommend the routine adoption in the NHS of the integrated multiplex PCR tests, xTAG Gastrointestinal Pathogen Panel, FilmArray GI Panel and Faecal Pathogens B assay, for identifying gastrointestinal pathogens in people with suspected gastroenteritis.” No study reported on change in management by test outcome, health-related quality of life, morbidity or mortality. They acknowledge the tests show promise but recommend further research on their effect on health outcomes and resource use. UpToDate somewhat tepidly recommends multiplex molecular testing “if culture is not available” (1). They suggest that any GPP positive for a bacterial pathogen be submitted for confirmatory culture and echo the call for caution relative to co-detections: “a high degree of clinical correlation is necessary when interpreting results of molecular testing since these assays detect genetic material, which does not always indicate infection with a viable organism, and identification of more than one pathogen is not uncommon.” Some commercial coverage of some highly multiplexed GPPs (> 5 targets) is either very restrictive (29), or absent (30,31).

In summary, studies and guidelines mostly agree that 1/ any diagnostic testing for AGE should be very selective since most cases are self-limited; 2/ multiplex GPPs can serve as an adjunct or alternative to conventional testing; and 3/ the increased sensitivity of highly multiplexed GPPs can be a double-edged sword, with targets of questionable clinical significance (even potentially nonviable), complicating interpretation. These new challenges, along with the potential for inappropriate testing, emphasize the need for enhanced diagnostic acumen, especially for more highly multiplexed GPPs. The greater the target number, the greater the interpretive complexity; the greater the interpretive complexity, the greater the need for clinician expertise and diagnostic stewardship.

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The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**
Note—Bolded diagnoses below have the highest utilization

Code	Description

These are new test so no top diagnosis codes to report. This will be updated once codes are available.

Visit **QuestDiagnostics.com/MLCP** to view current limited coverage tests, reference guides, and policy information.

To view the complete policy and the full list of medically supportive codes, please refer to the CMS website reference www.cms.gov ▶

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