

Gastrointestinal Pathogen Nucleic Acid Detection Panel Testing for Infectious Diarrhea

Policy Number: LABORATORY 028.3 T2
Effective Date: September 1, 2020

[Instructions for Use](#)

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Related Policies
None

Coverage Rationale

The following are proven and medically necessary:

- Multiplex polymerase chain reaction (PCR) panel testing of gastrointestinal pathogens of up to 5 targets when performed as part of an evaluation that includes blood cultures for an individual with any of the following:
 - Diarrhea for more than 7 days with fever and suspected bacteremia; or
 - Suspected enteric fever (i.e., typhoid or paratyphoid) in an individual with a history of recent travel to an endemic region (e.g., south-central Asia, Southeast Asia, and southern Africa) or who has consumed foods prepared by people with recent endemic exposure
- Multiplex PCR panel testing of gastrointestinal pathogens of up to 11 targets for the evaluation of persistent diarrhea in an individual with any of the following:
 - Diarrhea for more than 7 days with fever and suspected bacteremia, and the individual is at risk for *Clostridium difficile* (*C. difficile*) colitis; or
 - Acquired Immune Deficiency Syndrome (AIDS); or
 - On immunosuppressive medications following an organ transplant; or
 - Other condition causing immunosuppression and other stool diagnostic studies have failed to yield a pathogenic organism

Due to insufficient evidence of efficacy, multiplex PCR panel testing of gastrointestinal pathogens is unproven and not medically necessary for evaluating all other indications not listed above as proven and medically necessary.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information

Gastrointestinal Pathogen Nucleic Acid Detection Panel Testing for Infectious Diarrhea

Medical notes documenting all of the following:

- Current diagnosis
- History of illness and date of onset
- Co-morbidities
- Results of blood cultures and other lab tests
- Number of pathogen targets being tested
- Physician treatment plan based on the results of panel testing

Prior Authorization Requirements

Prior authorization is required in all sites of service.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
0097U	Gastrointestinal pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 22 targets (Campylobacter [C. jejuni/C. coli/C. upsaliensis], Clostridium difficile [C. difficile] toxin A/B, Plesiomonas shigelloides, Salmonella, Vibrio [V. parahaemolyticus/V. vulnificus/V. cholerae], including specific identification of Vibrio cholerae, Yersinia enterocolitica, Enteropathogenic Escherichia coli [EPEC], Enterotoxigenic Escherichia coli [ETEC] lt/st, Shiga-like toxin-producing Escherichia coli [STEC] stx1/stx2 [including specific identification of the E. coli O157 serogroup within STEC], Shigella/Enteroinvasive Escherichia coli [EIEC], Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia [also known as G. intestinalis and G. duodenalis], adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, sapovirus [Genogroups I, II, IV, and V])
87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., 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
87506	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., 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 (e.g., 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

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Description of Services

A variety of viruses, bacteria, and parasites can cause gastrointestinal (GI) infections. Testing for parasites and viral etiologies for community-acquired diarrhea is not necessary since this type of diarrhea is generally self-limited, managed by supportive care and hydration, and virus specific therapy is not available to treat this condition. After bacteria pathogens are ruled out, travelers' diarrhea with symptoms may require traditional ova and parasite stool examination and/or specific protozoa antigen or molecular testing.

Traditional methods of diagnosis include bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing. Culture-independent techniques have been developed 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 pathogens. In addition to single pathogen diagnostic tests, gastrointestinal (GI) pathogen nucleic acid detection panels simultaneously tests for the presence of multiple pathogenic microbes in a stool sample. (Palavecino, 2015)

Clinical Evidence

Freeman et al. (2017) conducted a systematic review of the evidence for the clinical effectiveness for three multiplex gastrointestinal pathogen panel (GPP) tests (xTAG, FilmArray and Faecal Pathogens B). Twenty three studies that included patients with acute diarrhea presenting at a community or hospital setting compared GPP tests with standard microbiology techniques. An evidential finding of the review is that GPP testing produces a greater number of pathogen-positive findings than conventional testing, but the clinical importance and consequence of these additional positive findings is uncertain. According to the authors, GPP testing can correctly identify the same positive cases as conventional methods but GPP testing adds more false positive results which cause unnecessary treatment and potentially a delayed return to normal activities. The authors stated that an additional limitation of GPP tests is that although the presence of bacterial pathogens is identified there is no bacterial culture to support either antimicrobial susceptibility testing or subtyping to support public health surveillance. Culturing from positive samples may be required to guide antimicrobial treatment or public health investigation when these are required.

In a prospective observational study, Keske et al. (2018) aimed to detect the etiological agents of acute diarrhea by a molecular gastrointestinal pathogen test (MGPT) and assessed the impact of MGPT on antimicrobial stewardship programs (ASP) for inpatients. Consecutive patients who had acute watery diarrhea and fever for more than 72 hours or acute bloody diarrhea, were included in the study. ASP was implemented in acute diarrhea cases and the outcomes were compared in the pre-ASP and post-ASP periods. An FDA-cleared multiplexed gastrointestinal PCR panel system, the BioFire FilmArray which detects 20 pathogens in stool, was used. In total, 699 patients were included. In 499 (71%) patients, at least one pathogen was detected, and 176 out of 499 (36%) were inpatients. The authors found that MGPT detected high rates of *C. difficile* in children and *Salmonella* spp., as well as relatively high rates of *Campylobacter* spp., which are hard to isolate by routine stool culture. According to the authors, using MGPT in clinical practice significantly decreased the unnecessary use of antibiotics. Inappropriate antibiotic use decreased in the post-ASP period compared with the pre-ASP period among inpatients (43% and 26%, respectively).

Beal et al. (2017) assessed the clinical impact of a comprehensive molecular test, the BioFire FilmArray gastrointestinal (GI) panel, which tests for common agents of infectious diarrhea in approximately 1 hour. Patients with stool cultures submitted were tested on the GI panel (n = 241 patients; 223 were hospitalized and 18 were evaluated in the emergency department) and were compared with control patients (n = 594) from the year prior. The most common organisms detected by the GI panel were enteropathogenic *Escherichia coli* (EPEC, n = 21), norovirus (n = 21), rotavirus (n = 15), sapovirus (n = 9), and *Salmonella* (n = 8). Patients tested on the GI panel had an average of 0.58 other infectious stool tests compared with 3.02 in the control group. The numbers of days on antibiotic(s) per patient were 1.73 in the cases and 2.12 in the controls. Patients with the GI panel had 0.18 abdomen and/or pelvic imaging studies per patient compared with 0.39 in the controls. The average length of time from stool culture collection to discharge was 3.4 days in the GI panel group versus 3.9 days in the controls. According to the authors, the GI panel improved patient care by rapidly identifying a broad range of pathogens which may not have otherwise been detected, reducing the need for other diagnostic tests, reducing unnecessary use of antibiotics, and leading to a reduction in hospital length of stay. This study suggests that the use of multiplex molecular panels result in an improvement in patient clinical outcomes in the setting of hospitalized patients with diarrhea.

Buss et al. (2015) evaluated the clinical validity of the FilmArray GI Panel and standard bacterial culture testing. In this cross-sectional study, prospectively collected samples submitted for stool culture were used to evaluate the clinical validity (n=1556). The majority of the specimens (86.8%) were collected from outpatients, with hospitalized and emergency room patients represented by 10.5% and 2.7% of the total study population, respectively. Cultures were set up within 4 days of specimen collection. FilmArray was performed by blinded BioFire personnel for comparator testing. With respect to standard methods of detection, results suggest that FilmArray is associated with sensitivities ranging from 94.5% to 100% and specificities ranging from 97.1% to 100% across pathogen types.

Khare et al. (2014) conducted a comparative evaluation of the FilmArray GI Panel and the Luminex xTag GI pathogen panel using stool samples submitted for routine GI testing such as culture, antigen testing, and individual real-time PCR 9 (n=500). The FilmArray GI Panel targeted 23 pathogens and the Luminex xTag panel targeted 11 pathogens. Of the samples tested, 230 were prospectively collected and 270 were retrospectively collected. Results suggest the sensitivity of FilmArray across targets ranged from 91.7% to 100% and the specificity ranged from 96.6% to 100% among the prospectively collected specimens. Sensitivity ranged from 95.8% to 100% and specificity ranged from 90.8% to 100% for xTAG. Several targets had lower sensitivity for the retrospectively analyzed samples. Although more than half of the samples were retrospectively analyzed with multiplex assay, data was provided separately for the prospective and retrospective samples.

Professional Societies

American College of Gastroenterology (ACG)

The 2016 ACG Clinical Guidelines for Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults makes the following diagnosis recommendations: (Riddle et al., 2016)

- 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).

Infectious Diseases Society of America (IDSA)

The 2017 IDSA Practice Guidelines for the Diagnosis and Management of Infection Diarrhea list the following recommendations: (Shane et al., 2017)

- People with fever or bloody diarrhea should be evaluated for enteropathogens for which antimicrobial agents may confer clinical benefit, including *Salmonella enterica* subspecies, *Shigella*, and *Campylobacter* (strong recommendation, low level of evidence).
- Enteric fever should be considered when a febrile person (with or without diarrhea) has a history of travel to areas in which causative agents are endemic, has had consumed foods prepared by people with recent endemic exposure, or has laboratory exposure to *Salmonella enterica* subspecies *enterica* serovar Typhi and *Salmonella enterica* subspecies *enterica* serovar Paratyphi (strong recommendation, moderate level of evidence).
- Stool testing should be performed for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, and STEC in people with diarrhea accompanied by fever, bloody or mucoid stools, severe abdominal cramping or tenderness, or signs of sepsis (strong recommendation, moderate level of evidence). Bloody stools are not an expected manifestation of infection with *C. difficile*. (strong recommendation, moderate level of evidence).
- Stool testing should be performed under clearly identified circumstances for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, and STEC in symptomatic hosts (strong recommendation, low level of evidence). Specifically,
 - Test for *Yersinia enterocolitica* in people with persistent abdominal pain (especially school-aged children with right lower quadrant pain mimicking appendicitis who may have mesenteric adenitis), and in people with fever at epidemiologic risk for yersiniosis, including infants with direct or indirect exposures to raw or undercooked pork products.
 - In addition, test stool specimens for *Vibrio* species in people with large volume rice water stools or either exposure to salty or brackish waters, consumption of raw or undercooked shellfish, or travel to cholera-endemic regions within 3 days prior to onset of diarrhea.
- 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 recommendation, moderate level of evidence).
- 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 recommendation, moderate level of evidence).

- Blood cultures should be obtained from infants younger than 3 months of age, people of any age with signs of septicemia or when enteric fever is suspected, people with systemic manifestations of infection, people who are immunocompromised, people with certain high-risk conditions such as hemolytic anemia, and people who traveled to or have had contact with travelers from enteric fever–endemic areas with a febrile illness of unknown etiology (strong recommendation, moderate level of evidence).
- 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 recommendation, moderate level of evidence).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

There are several commercial multiplex polymerase chain reaction (PCR) kits that have been cleared through the FDA 510(k) clearance process. These include xTAG gastrointestinal pathogen panels (GPPs); FilmArray Panels; Verigene panels; and BioCode GPPs.

To locate marketing clearance information for a specific panel, search the FDA 510(k) premarket notification database available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> (use Product Codes PCH and PCI).

Accessed September 17, 2019

References

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2020T0604B]

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Policy History/Revision Information

Date	Summary of Changes
09/01/2020	<p>Template Update</p> <ul style="list-style-type: none">● Reformatted policy; transferred content to new template● Removed and replaced section titled <i>Conditions of Coverage</i> with <i>Prior Authorization Requirements</i><ul style="list-style-type: none">○ Simplified and relocated language pertaining to prior authorization guidelines○ Removed language addressing benefit type and referral requirements (refer to the member specific benefit plan document)● Replaced references to “precertification” with “prior authorization” <p>Supporting Information</p> <ul style="list-style-type: none">● Archived previous policy version LABORATORY 028.2 T2

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.