Gastrointestinal Pathogen Nucleic Acid Detection Panel Testing for Infectious Diarrhea (for Idaho Only)

Policy Number: CS169ID.A
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Instructions for Use

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Related Policies
None

Application

This Medical Policy only applies the state of Idaho, including Idaho Medicaid Plus plans.

Coverage Rationale

The following are proven and medically necessary:

- Multiplex polymerase chain reaction (PCR) panel testing of gastrointestinal pathogens including up to five targets when performed as part of an evaluation that includes blood cultures for an individual with any **one** of the following:
  - Diarrhea for more than 7 days; or
  - Diarrhea with at least **one** of the following:
    - Fever; or
    - Bloody or mucoid stools; or
    - Severe abdominal cramping or tenderness; or
    - Signs of sepsis

    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, South East Asia, and Southern Africa) or who has consumed foods prepared by people with recent endemic exposure
- Multiplex PCR panel testing of gastrointestinal pathogens including up to 11 targets for the evaluation of persistent diarrhea in an individual with any **one** of the following:
  - At risk for *Clostridium difficile* (*C. difficile*) colitis and **one** of the following:
    - Diarrhea for more than 7 days; or
    - Diarrhea with at least **one** of the following:
      - Fever; or
      - Bloody or mucoid stools; or
      - Severe abdominal cramping or tenderness; or
      - Signs of sepsis

    or
  - Acquired Immune Deficiency Syndrome (AIDS); or
  - On immunosuppressive medications either following an organ transplant or when used for treatment of an auto-immune disease; 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.

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 federal, state, or contractual requirements 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 and Guidelines may apply.

CPT Code	Description
0369U	Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique
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

Description of Services

A variety of viruses, bacteria, and parasites can cause gastrointestinal (GI) infections and diarrhea. Most instances of acute diarrhea are self-limited and can be managed by supportive care and hydration. For persistent diarrhea or more severe symptoms such as fever or bloody stools, testing for the cause of diarrhea may be necessary in order to facilitate appropriate treatment (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDKD], 2016).

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

Clinical Evidence

Multiplex Polymerase Chain Reaction (PCR) Panel Testing

In an unblinded, randomized controlled trial, Xie et al. (2023) investigated whether the use of a large multiplex stool diagnostic panel test (BioFire FilmArray® 22 pathogen gastrointestinal panel) impacted the practice of pediatric emergency medicine physicians when providing care to children with hematochezia seen in a pediatric emergency room. The study included 60 children with acute hematochezia, ages six months to eighteen years, randomized into two cohorts; one including those whose stool was tested with standard microbiologic methods and another including those whose stool was tested using the BioFire FilmArray panel. The primary outcome was the performance of any blood tests (e.g., complete blood count) within a 72-hour timeframe. Study results showed that the time to results were reduced for

individuals in the BioFire FilmArray group [median 3 hours with interquartile range (IQR) of 3-4 hours, versus 42 hours (IQR 23.5 to 47.3 hours); difference of -38 hours, 95% confidence interval (CI) of -41 to -22 hours]. A total of 65% of individuals in the BioFire FilmArray group were found to have a detectable pathogen per the BioFire FilmArray test. In the same group, 37% of the children had a detectable pathogen by standard testing. Although a greater number of bacteria were found in paired samples from children in the BioFire FilmArray group when using the BioFire FilmArray vs. standard-of-care testing, the added knowledge of these pathogens was not found to have significant clinical impact. In the standard-of-care group, 35% of children had an identified pathogen. In the BioFire FilmArray arm, the most frequent pathogen found was enteropathogenic *Escherichia coli* (EPEC) (19%), followed by *Campylobacter* (16%), and *Salmonella* (13%). The standard-of-care group findings included *Campylobacter* spp. (20%), *Salmonella* spp. (9), two individuals with *Escherichia coli* (*E. coli*) O157:H7, and one child who was found to have a non-O157 Shiga toxin-producing *E. coli* (STEC). Overall, the two groups showed no difference in primary outcome: In the BioFire FilmArray group, 52% of participants had blood testing within 72 hours and in the standard-of-care group, 62% had blood tests within 72 hours (difference of -10.5%, 95% CI of -35.4 to 14.5%). In addition, no differences were found between the groups related to administration of intravenous fluid, antibiotic treatment, hospitalization or diagnostic imaging. The BioFire FilmArray test was not associated with clinically significant reduction in the utilization of health care resources or improved clinical outcomes in the participants of this study. This study was limited by the small sample size and lack of blinding as well as focus on only children with diarrhea including hematochezia, which impacts overall generalizability. The authors advise that education regarding the implementation of gastrointestinal panel testing is needed to improve integration of this technology into clinical care and further large, multicenter studies are recommended.

In another study focused on use of the BioFire FilmArray Gastrointestinal Panel, Carmon et al. (2023) used FilmArray to evaluate gastrointestinal infection and distribution of pathogens in the stool samples of 91 hospitalized participants in a medical center in Israel. The clinical and demographic information of those with negative and positive samples was also compared. Sixty-one total samples were considered positive. The most commonly identified pathogen was *Campylobacter* (34.4%), followed by *Salmonella* (24.6%), enteroaggregative *E. coli* (EAEC) (19.7%) and EPEC (16.4%). Of note, 37.7% of the individuals who tested positive had multiple pathogens detected; most commonly EAEC and EPEC (total of 17.4% of those with multiple pathogens detected). Significantly higher use of antibiotics post-diagnosis (63.9% vs. 36.7%; $p = 0.014$), shorter length of stay and time to discharge ($p = 0.035$, $p = 0.003$, respectively) and slightly younger age ($p = 0.012$) were associated with positive test results in this study. The authors concluded that the use of FilmArray led to earlier identification of causal infectious drivers and improved clinical outcomes. The study was limited due to the retrospective nature of the analysis as well as the small sample size. Further high-quality studies with larger sample numbers are recommended to determine the overall benefit of gastrointestinal panel testing.

Aiming to investigate infectious agents responsible for chronic diarrhea in individuals newly diagnosed with human immunodeficiency virus (HIV), Montalvo-Otivo et al. (2023) conducted an observational, cross-sectional study. The study included 24 individuals newly diagnosed with HIV that met inclusion criteria including age greater than 18 years, HIV infection, watery diarrhea for greater than four weeks, a CD4 T lymphocyte count, and viral load for HIV. The BioFire FilmArray 22 pathogen gastrointestinal panel was used to test samples from the participants. Of the 24 samples collected, 92% were considered positive with bacteria found in 69%, parasites found in 18%, and viruses found in 13%. EPEC and EAEC were the most frequently identified bacteria. The parasite *Giardia lamblia* was found in 25% of the samples, and norovirus was the most frequent viral agent, in 33% of the samples. The median number of infectious agents found in individual participants was three. Biologic agents not identified with FilmArray included *tuberculosis* and fungi. The researchers indicate that their results support the use of FilmArray to identify multiple pathogens related to diarrhea via a single test in individuals affected with HIV, as it to earlier diagnosis and treatment. They recommend continued use of conventional studies as well (e.g., parasite exams with special dyes and the modified Ziehl-Neelsen staining) since FilmArray is not able to identify some specific opportunistic agents that may be present in individuals with HIV and stress the importance of investigation of nonidentified agents through methods such as colonoscopy. The study is limited due to its observational approach and small sample size.

In a 2023 joint report, the Association for Molecular Pathology (AMP), American Society for Microbiology (ASM), Infectious Diseases Society of America (IDSA) and Pan American Society for Clinical Virology (PASCV) addressed the utility of multiplex panel molecular testing for the diagnosis of infection in various body sites (Lewinski et al.) With regard to gastrointestinal pathogen testing, the authors note that while molecular testing methods have been shown to improve detection when compared with culture, the value of multiplex testing of gastroenteritis and foodborne disease has been questioned due to the cost and continues to be studied. The benefits of syndromic multiplex panels when compared with culture-based diagnostic methods, including more rapid detection (and therefore, more rapid treatment) and the ability to detect pathogens that may require specialized techniques for culture are addressed. However, limitations are noted as well. These include the restriction of panels to specific organisms and the ability of multiplex panel testing to detect nucleic acid from both living and dead organisms. Overall, the authors state that multiplex approaches to diagnosis of infection are generally well-established with benefit, but questions remain regarding such items as the size of testing panels and

potential for algorithmic approaches to maximize benefits to affected individuals and their providers. Further study is recommended.

In 2022, Truong et al. (included in the Hayes report below) performed a comparative study assessing the impact of multiplex gastrointestinal PCR testing (GI-PCR) on the management of infectious diarrhea in children. A GI-PCR panel test (BioFire FilmArray) was performed on each stool sample from 172 children. Data was collected on the children's clinical management prior to and after GI-PCR results. The primary criteria for performing stool analysis were mucous/bloody diarrhea and or traveler's diarrhea (n = 130). GI-PCRs were positive for 120 total participants (70%). The most common pathogens identified were EAEC (n = 39; 23%), EPEC (n = 34; 20%), Shigella/enteroinvasive E. coli (EIEC) (n = 27; 16%) and *Campylobacter* (n = 21; 12%). When compared with stool cultures, GI-PCR detected 21 vs. 19 *Campylobacter*, 12 vs. 10 *Salmonella,* 27 Shigella/EIEC vs. 13 *Shigella*, 2 vs. 2 *Yersinia enterocolitica*, and 1 vs. 1 *Plesiomonas shigelloides*, respectively. Medical management was revised for 40 children (23%) based on GI-PCR results, prior to results from stool cultures being available. The authors concluded that GI-PCR results impacted the medical management of gastroenteritis for almost a quarter of the children and particularly the use of the appropriate antibiotic treatment prior to stool culture results.

A prospective, randomized, cohort study was performed in 2022 by Montasser et al. evaluating the use of multiplex PCR for rapid detection of four major intestinal pathogens that cause gastroenteritis. The study included 200 stool samples from participants; pathogens were identified using both molecular diagnostics and stool cultures. The identified organisms using conventional cultures were *Shigella* (27%), *Aeromonas* species (10%), and *enterohemorrhagic E. coli* (EHEC) O157 (8%). When using multiplex PCR, *Shigella* was again the most common pathogen (detected in 40.5% of positive samples) followed by *Aeromonas* (30%), EHEC (20%) and *Campylobacter* species (1%). Diagnostically, multiplex PCR showed sensitivity of 100% for *Shigella*, EHEC and *Aeromonas* with specificity of 88.5%, 92.4% and 77.8%, respectively, related to conventional methods. The diagnosis of *Campylobacter* showed specificity of 99% and negative predictive value (NPV) of 100%. In conclusion, the researchers asserted that multiplex PCR is an quick and accurate method of detection of common intestinal pathogens causing severe gastroenteritis.

In an effort to further investigate potential quality improvements in clinical management, use of antibiotics, and in-hospital infection transmission in children with acute diarrhea, Yoo et al. (2021) analyzed use of the BioFire® FilmArray® Gastrointestinal Panel (GI Panel) in a prospective study with a matched historical cohort. Participants in the prospective study included children younger than 19 years of age with new onset diarrhea. A 1:1 matched historical cohort of children diagnosed with acute gastroenteritis (AGE) during the 4 years prior to this investigation was analyzed as well. Children in the prospective cohort received stool testing using the GI Panel in addition to conventional methods. A total of 182 individuals with suspected infectious diarrhea were included in the prospective cohort. The median age was 3.8 years and 64.3% were male. Participants in this cohort were divided into two subgroups: community-onset diarrhea (85.7%) and hospital-onset diarrhea (14.3%). The GI panel had a higher pathogen-positivity rate for community-onset diarrhea (58.3%) compared to both conventional studies (42.3%) and in the historical cohort (31.4%). Reporting time after admission averaged 25 hours for the GI panel and 72 hours for the historical cohort. In addition, there was a reduction in antibiotic use in the prospective cohort compared to the historical cohort (35.3% vs. 71.8%). In the prospective cohort, 126 different pathogens from 91 stool samples were identified by the GI panel and in the historical cohort, 51 pathogens were identified from 49 stool samples. Of the 26 patients with hospital-onset diarrhea, a single pathogen was detected in 64.3% of the children and two or more pathogens were detected in 35.7%. Test results were used to make clinical decisions regarding isolation/precaution measures in-hospital. However, there were discrepancies between the results of the GI panel and traditional, routine testing in the prospective cohort; although the GI panel showed high detection rates of the pathogens included in the panel, 50% of the pathogens that were positive in the standard conventional studies and negative in the GI Panel were bacteria that are not included in FilmArray, but rather cultured from stool, highlighting the importance of stool cultures in the pathogenic diagnosis of AGE. The authors concluded that the rapid turnaround time of the GI Panel test and the high positivity rate of the panel demonstrates clinical benefit for children with acute diarrhea, including potentially reducing the use of antibiotics and enabling early use of infection precautions and/or isolation.

Chang et al. (2021) performed a systematic review and meta-analysis comparing and evaluating accuracy of the BioFire FilmArray and Luminex xTAG multiplex PCR gastrointestinal (GI) panels. Eleven studies including a total of 7,085 stool samples met eligibility criteria. The FilmArray panel demonstrated higher sensitivity (> 0.90) than xTAG GPP (0.81-0.95) for the majority of pathogens, with the exception of Rotavirus A (equal sensitivity). Overall, multiplex PCR testing was highly accurate with a specificity ≥ 0.98 for all pathogens except *Yersinia enterocolitica*. According to the study results, xTAG GPP and FilmArray GI panel accurately detected more than 90% of common enteropathogens with high sensitivity, specificity, and a shorter turnaround time. As such, the researchers state that multiplex platforms can have a significant impact on clinical management by reducing the time to identify a pathogen, influencing outcome by initiating treatment earlier, altering anti-microbial stewardship, and optimizing infection control. Although this systematic review included a large volume of samples and robust analysis following the Cochrane guideline, there are limitations in the review. The

data on FilmArray was relatively few and did not allow subgroup analyses for some rare pathogens. In addition, the patient characteristics such as age, symptoms, and travel history varied among the studies that were included, and the number of studies (11) may be insufficient for some of the sensitivity analyses. There were also five studies that included discordant analysis which could increase the sensitivity and specificity due to potentially elevating the true positive and negative cases. Studies by Huang et al. (2016) and Khare et al. (2014), previously discussed in this policy, and Buss et al. (2015), discussed below, were included in this systematic review and meta-analysis.

Machiels et al. (2020) published results of a cross-sectional study evaluating clinical impact of using BioFire FilmArray, a broad, multiplex gastrointestinal panel, on individuals with gastroenteritis in a Dutch tertiary care center. FilmArray was tested in parallel with either one or a combination of standardly performed PCR panel tests based on clinical symptoms and history of illness. Testing was performed on 182 individuals. FilmArray detected one or more pathogens in 39.6% of the participants and routine testing detected one or more pathogens in 28.6% of the participants. Time to receive results, including transport time, decreased from a median of 53 hours for the standard testing to 16 hours for FilmArray. The authors state that this decrease in time to receive results could have resulted in 3.6 saved antibiotic days, earlier (29 hours) removal from isolation for 26 patients, and prevention of additional imaging in five patients. Limitations of this study include the small sample size, retrospective design and the single-site of testing.

A 2020 systematic review and meta-analysis by Meyer et al. sought to analyze and report the pathogens identified through the use of a multiplex molecular array (BioFire FilmArray) in individuals with gastroenteritis. Publications reporting pathogens that had been identified via FilmArray were searched and the proportions of pathogens identified were then pooled. A total of 14 studies including 17,815 patients were included in the analysis. Of these, 39% (7,071) had positive FilmArray results. In addition, 18.1% of individuals had co-infections with more than one pathogen. Pathogens identified were as follows, in order of frequency: EPEC (27.5%), *Clostridium difficile* (19.3%), Norovirus (15.1%), EAEC (15%), *Campylobacter* spp. (11.8%), *Salmonella* spp. (8.1%), ETEC (7.3%), rotavirus (7.3%), sapovirus (7.1%), STEC (5.2%), *Shigella*/EIEC (4.9%), *Giardia lamblia* (4%), adenovirus (3.8%), *Cryptosporidium* spp. (3.8%), astrovirus (2.8%), *Yersinia enterocolitica* (1.7%), E. coli O157 (1.1%), *Plesiomonas shigelloides* (1.1%), *Cyclospora cayetanensis* (0.7%), *Vibrio* spp. (0.5%), *Vibrio cholerae* (0.3%) and *Entamoeba histolytica* (0.3). FilmArray was able to identify one or more pathogens in 48.2% of individuals tested versus 16.7% using standard conventional diagnostics in the studies that had control groups with microbiological examination of stool performed using methods other than FilmArray. The authors indicate that although the FilmArray panel was positive in 39.7% of patients with gastroenteritis, the carriage rates of identified organisms must be considered. They further propose that restricted ordering of molecular panels specific to those patients who might benefit from targeted treatment could provide clinical value by quickly identifying the pathogen and treating appropriately, and that future studies should focus on determining which of the identified pathogens in a test result are responsible for symptoms present and whether co-infections are associated with a more severe disease presentation. Studies by Beal et al. (2017), Axelrad et al. (2019), and Khare et al. (2019), previously discussed in this policy, and Buss et al. (2015), Pouletty et al. (2019), and Leli et al. (2020), discussed below, were included in this systematic review and metanalysis.

Leli et al. (2020) evaluated and compared the diagnostic yield of the FilmArray gastrointestinal panel to that of routine stool culture for etiological diagnosis of infectious diarrhea. Stool samples (n = 183) collected as part of routine care from March 2016 to March 2019, were included in this retrospective analysis. Samples were then cultured and tested by FilmArray and the following results from the comparison of diagnostic accuracy between culture and FilmArray with respect to *Campylobacter*, *Salmonella, Shigella, Yersinia enterocolitica* and STEC 0157 were reported: 100% (95% CI: 85-100%) sensitivity; 93.4% (95% CI: 87.9-96.6%) specificity; 74.3% (95% CI: 57.5-86.4%) positive predictive value; 100% (95% CI:96.7-100%) negative predictive value; 2.9% (95% CI: 1.6-5.1) positive likelihood ratio; zero negative likelihood ratio. The FilmArray gastrointestinal panel identified 34.5% more pathogens than traditional culture methods (p = 0.001). The authors concluded that FilmArray identified a spectrum of pathogens and had good diagnostic performance when compared to standard culture for the diagnosis of infectious diarrhea. However, the study lacks clinical data and was performed in a single site in a community hospital setting, thus the pathogen detection rate cannot be completely generalized and positive results for *Clostridium difficile* (*C. difficile*) and viruses were not confirmed with alternative or reference methods.

Pouletty et al. (2019) utilized multiplex PCR on stool samples to determine pathogen distribution of traveler's diarrhea (TD) in children traveling from tropical countries. From August 2014 to October 2015, children with TD admitted to two university hospitals were included in the prospective study. The FilmArray GI PCR panel was used to identify 22 pathogens. Comparisons for the detection of *Salmonella, Shigella* and *Campylobacter* by PCR and culture were made. Prevalence of extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae was also evaluated. In 58 (98%) of the 59 children, at least one pathogen was recognized. This included 9 enteropathogenic bacteria, 5 viruses and 2 parasites. The detection of enteropathogenic bacteria by multiplex PCR was enhanced by 25%. EAEC (n = 32), EPEC (n = 26), enterotoxigenic E. coli (ETEC) (n = 19), *Salmonella enterica*/EIEC/*Shigella* (n = 16 each), *Cryptosporidium*,

sapovirus (n = 11 each), *Campylobater jejuni*, norovirus (n = 10 each), rotavirus (n = 9), *Giardia* (n = 8) and STEC (n = 4) were the most frequent pathogens identified. Co-infections (n = 52) were reported including bacteria and viruses (n = 21), multiple bacteria (n = 14), or bacteria and parasites (n = 10). ESBL were found in 28 cases. The authors concluded that PCR performed on stools demonstrated a high prevalence of diverse enteric pathogens and coinfections in children with TD. Multiplex PCR optimized the number of treated patients by 27% compared with culture. The authors concluded that because major enteropathogenic bacteria were detected more often by PCR, the technique may allow earlier and more appropriate antibiotic treatment and increase the number of correctly diagnosed patients. Noted limitations of this study include the lack of controls involving traveling children without diarrhea and non-traveling children, the lack of PCR testing for all the children admitted for TD, and patient recruitment solely from the emergency department (these children likely had more severe symptoms). Lastly, comparison of this study's results with other existing studies should be considered cautiously, as techniques and pathogens detected were not the same.

The Seegene Allplex Gastrointestinal, Luminex xTAG Gastrointestinal Pathogen Panel, and BD MAX™ Enteric Assays were compared by Yoo et al. (2019) to determine efficiency of gastrointestinal pathogen detection from 858 clinical stool samples. Positive percentage agreements of Seegene, Luminex, and BD MAX were 94% (258 of 275), 92% (254 of 275), and 78% (46 of 59), respectively. Luminex showed a low negative percentage agreement for Salmonella (n = 31). For viruses, positive/negative percentage agreements of Seegene and Luminex were 99%/96% and 93%/99%, respectively. The authors suggested that these assays are promising for the detection of gastrointestinal pathogens simultaneously.

A prospective study from the Alberta Provincial Pediatric Enteric Infection Team was conducted by Kellner et al. (2019) between December 2014 and March 2018, to determine agreement for the bacterial pathogens of interest between stool bacterial culture methods and the Luminex xTAG gastrointestinal pathogen panel (GPP). The primary outcome was bacterial pathogen detection agreement from a cohort of 3,089 children with gastroenteritis. This was measured as overall percent agreements, positive percentage agreement (PPA), and Cohen's K, between stool bacterial culture and the GPP for bacterial pathogens sought by both detection methods: *Campylobacter* spp., *E.coli* 0157, *Salmonella* spp. and *Shigella* spp. A secondary analysis targeted *Salmonella* spp. which included phenotype assessment, additional testing of GPP-negative/culture positive isolate suspensions with the GPP, and in-house and commercial confirmatory nucleic acid testing of GPP positive/culture negative extracts. The overall percentage agreement between the two testing methods was > 99% for each individual pathogen and 98.9% (95% CI, 98.5%,99.3%) for all combined pathogens. Overall, PPA was 83% (73/88; 95% CI, 73.1%,89.8%). Cohen's K was > 0.70 for *E.coli* 0157, *Shigella* spp. and *Salmonella* spp. and 0.89 for *Campylobacter* spp. *Salmonella* spp., the most frequently identified pathogen, was detected from the samples of 64 patients; 12 (19%) by culture only, 9 (14%) by GPP only, and 43 (67%) by both technologies. Positive percent agreement for *Salmonella* spp. was 78.2% (95% CI 64.6%, 87.8%). Isolate suspensions from 12 patients with GPP negative/culture positive for *Salmonella* tested positive by GPP. GPP positive/culture negative samples tested positive using additional assays for 0/2 *Campylobacter*-positive specimens, 0/4 *E.coli* 0157-positive samples, 0/9 *Salmonella*-positive samples and 2/3 *Shigella*-positive samples. For rectal swab and stool samples, the median cycle threshold (C_T) values, determined using quantitative PCR, were higher for GPP-negative/culture positive samples than for GPP-positive/culture positive samples [for rectal swabs, 36.9% (interquartile range [IQR], 33.7, 37.1) vs. 30 (IQR, 26.2, 33.2), respectively (p = 0.002); for stool samples, 36.9 (IQR, 33.7, 37.1) versus 29.0 (IQR, 24.8, 30.8), respectively (p = 0.001)]. The authors concluded that GPP overall had high concordance with culture methods, however, the PPA was suboptimal for shared bacterial targets. *Salmonella* spp. identification by GPP had a propensity for false positives and negatives. Therefore, the accuracy of GPP and other nucleic-acid amplification (NAAT) assays requires further studies to determine clinical validity and utility before culture replacement is considered.

The clinical validity of molecular testing for adult outpatients with diarrhea and the validation of the Infectious Disease Society of America (IDSA) 2017 testing recommendation was the primary objective of Clark et al. (2019). The IDSA recommends FDA-approved molecular testing panels for increased sensitivity and decreased turn-around times vs. bacterial cultures for the detection of enteric pathogens even though these molecular methods have not proven cost-effective and may not have a significant effect on clinical management. A retrospective chart review from the University of Virginia was performed for 629 samples using the FilmArray Gastrointestinal Panel for adults with diarrhea between March 2015 and July 2016. This review revealed that 127/629 (20.2%) of specimens had a detected pathogen; the most common identified were EPEC (47, 7.5%), norovirus (24, 3.8%), EAEC (14, 2.2%), *Campylobacter* (9,1.4%) and *Salmonella* (9, 1.4%). Clinical yield was low, resulting in antimicrobial treatment indicated for 18 (2.9%) of patients and any change in clinical management indicated for 33 (5.2%) of patients. Following the 2017 IDSA guidelines which recommend diagnostic testing for patients with fever, abdominal pain, bloody stool, or an immunocompromising condition, would have reduced testing by 32.3% without significantly reducing clinical yield (sensitivity, 97%; 95%CI, 84.2%-99.9%; negative predictive value, 99.5%; 95% CI, 97.3%-100.0%). In conclusion, the authors claimed that the IDSA guidelines were validated as sensitive but not specific clinical criteria for the use of diagnostic testing and demonstrated that following these guidelines could reduce testing by one-third without reducing clinical yield.

Beckman and Ferrieri (2019) compared the integrity of Verigene Enteric Pathogens (PCR/microarray) test to traditional enteric culture methods for identifying *Salmonella* and *Shigella* from stool samples from February 2016 to August 2016. Positive bacterial pathogen samples underwent confirmatory cultures. Valid results were in 3,767/3,795 (99.3%) samples; 487 (13.2%) were positive for at least one bacterial and/or viral pathogen by Verigene and 45.5% tested positive for one or more bacterial pathogens. The most frequently identified pathogens by PCR/microarray were norovirus (50.3%), *Campylobacter* (18.3%), *Salmonella* (13.7%) and *Shigella* (5.8%). Agreement between positive culture-based testing and PCR/microarray was 85.3%. PCR/microarray testing revealed 95.2% and 87.5% sensitivity and 99.8% and 99.8% specificity for *Salmonella* and *Shigella*, respectively, compared with cultures. Based on their findings, the authors surmised that the Verigene PCR/microarray platform reliably produced valid stool-test results for common bacterial/viral causes of acute diarrhea in addition to detecting pathogens not identified using culture-based methods.

Performance characteristics of PCR for the detection of *Salmonella* compared to the gold standard of culture were evaluated by Hapuarachchi et al. (2019). The sensitivity and specificity of PCR using the BD MAX Enteric Bacterial Panel was compared to those of enrichment culture during a nine-month prospective comparative study; all stool samples underwent both PCR and culture for *Salmonella*. Selenite enrichment culture for *Salmonella* was confirmed using the API 10S and serotyping. A sample size of 6,372 stool culture and PCR pairs were studied. The *Salmonella* prevalence was reported as 1.2%. The sensitivity, specificity, positive predictive value and negative predictive value of PCR vs. culture was 89% (67/75), 99.8% (6286/6297), 86% (67/78) and 99% (6286/6294), respectively. The authors concluded that the enrichment culture was substantially more sensitive than PCR using BD Max for identifying *Salmonella* in stool samples and recommended that when PCR testing is used for detection of enteric pathogens, enrichment culture testing for salmonella be performed in parallel.

Tilmanne et al. (2019) compared the results of molecular testing methods and routine diagnostic methods for the detection of acute gastroenteritis (AGE) in symptomatic children and asymptomatic controls. A total of 178 patients admitted to a pediatric emergency department from two hospitals in Brussels from May 2015 to October 2016 were included in the study; 165 asymptomatic controls originated from the same hospitals. Stool samples were taken from all participants and analyzed for common pathogenic bacteria (culture), virus (immunochromatography) and parasites (microscopy). The Luminex Gastrointestinal Pathogen Panel was used for the detection of common enteropathogens using multiplex-PCR. An enteropathogen was detected in 62.4% (111/178) of cases when combining the two methods [56.2% (100/178) by Luminex, 42.7% (76/178) with routine methods] and 29.1% (48/165) of controls [24.2% (40/165) by Luminex and 10.3% (17/165) by routine methods]. *Campylobacter*, *Shigella*, and *Yersinia* were missed by Luminex, but detected by culture method. However, Luminex detected *Salmonella* more often than routine methods [29/178 (16.3%) vs. 7/178 (3.9%), $p < 0.05$]. The authors raised concerns about the pathogens missed by Luminex vs. those detected by culture. While the high positivity and rapid turnaround time for diagnosis of AGE by Luminex is promising, their concern was noted regarding difficulty of result interpretation due to high positivity rates in cases and controls.
In a 2018 Molecular Test Assessment (updated in 2022), Hayes conducted an evaluation of multiplex molecular panels for gastrointestinal infections. The report addressed tests including xTAG (15 targets), FilmArray (22 targets), Verigene (9 targets) and BioCode (17 targets) and found an overall low body of evidence related to study quality, lack of a clear, ideal standard test and a lack of evidence regarding clinical utility. However, the report notes that based on the evidence reviewed, xTAG and FilmArray panels showed high clinical validity for most of the available pathogenic targets compared to conventional testing methods. Evidence for clinical utility was more limited. Additionally, although multiplex panels are likely to better detect co-infections, several of the targets in the test were rarely detected (e.g., Vibrio spp. and Yersinia entercolitica), making evaluation of clinical validity for those tests impossible.

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 assess the impact of MGPT on antimicrobial stewardship programs (ASP) for inpatients. Consequent 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 most commonly detected pathogens in acute diarrhea were EPEC, EAEC, ETEC, Norovirus, STEC, and *Campylobacter* species. Notably, the authors found that MCPT detected high rates of *C. difficile* in children and *Salmonella* spp., as well as relatively high rates of *Campylobacter* spp., which are typically 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). However, this was a single center study. In addition, the authors state that the detection of pathogens using MGPT does not mean that the detected pathogen is the cause of diarrhea, so test results should be interpreted carefully.

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. Studies by Khare et al. (2014), previously discussed in this policy and Buss et al. (2015), discussed below, were included in this systematic review.

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 = 1,556). 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.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

In 2021, Kelly et al. published an ACG clinical guideline addressing C. difficile. This guideline recommends that “C. difficile infection (CDI) testing algorithms should include both a highly sensitive and highly specific testing modality to help distinguish colonization from active infection.” The guideline also points out that because nucleic acid amplification testing (NAAT) cannot distinguish asymptomatic colonization from active infection, use of a 2-step algorithm is preferred for optimal diagnostic accuracy.

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)

American Society for Microbiology (ASM)

In 2019, ASM published a guideline addressing the clinical utility of multiplex tests for respiratory and GI pathogens. The guideline states that multiplex molecular panel tests provide the ability to test a single sample for multiple pathogens quickly and with high accuracy. Further noted, however, is the lack of outcome-based evidence supporting direct benefit to clinical care. Despite this evidence, the ASM guideline asserts that these tests improve patient care by providing accurate results on a timeline that allows actions positively impacting care of affected individuals such as the timely initiation of appropriate therapies which may lead to less transmission of disease, shortened duration of symptoms, and a decrease in the need for additional testing. Non-medical interventions (e.g., isolation) can also be impacted by the detection of pathogens and for those individuals with infections that do not require an intervention, multiplex tests assist providers in determining when antibiotics should not be administered.

American Society of Transplantation Infectious Diseases Community of Practice

La Hoz and Morris (2019) recommended that “for the diagnosis of SOT (solid organ transplant) recipients with suspected gastrointestinal infections”, gastrointestinal multiplex molecular assays are recommended to identify *Cryptosporidium*, *Cyclospora, and Giardia*.

Infectious Diseases Society of America (IDSA)

An IDSA Clinical Practice Guideline for Laboratory Diagnosis of Infectious Diseases (Miller, 2018) includes the following statements on culture-independent NAATs: “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. Culture-independent methods should not be used as test of cure as they will detect both viable and nonviable organisms." The guideline also acknowledges that culture independent testing methods have a faster turnaround time than culture and have been reported to be more sensitive than culture, resulting in higher rates of detection.

The 2017 IDSA Practice Guidelines for the Diagnosis and Management of Infectious 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, but are not limited to, 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 October 13, 2023)

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Policy History/Revision Information

Date	Summary of Changes
06/01/2025	• New Medical Policy

Instructions for Use

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

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical 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.