LCD - Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Amplification Techniques (NAATs) (L38227)

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Contractor Information

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Issue

Issue Description

Analysis of claims data identified an increase in jurisdictional utilization of Gastrointestinal Pathogen Panels (GIP) of 12 or greater targets resulting in utilization being above the national average. This revised LCD provides limited coverage for outpatient testing of GIP panels utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs) for Medicare beneficiaries with acute or persistent diarrhea with signs or risk factors for severe disease, and for Medicare beneficiaries that have an immunocompromising medical condition with acute or persistent diarrhea as outlined in the LCD. GIP panels utilizing multiplex NAATs are considered not medically reasonable and necessary for: testing for cure, testing of asymptomatic patients, repeat testing of patients using GIP panels within seven days during the same episode of diarrhea, or performance of more than one GIP panel on the same date of service by the same or a different provider.

Issue - Explanation of Change Between Proposed LCD and Final LCD

Limitation #1 has been revised, in response to a comment that was received, to make it clear that testing for a cure is not considered medically reasonable and necessary.

CMS National Coverage Policy

This LCD supplements but does not replace, modify, or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for GIP panels utilizing multiplex NAATs. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy and are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify, or supersede applicable state statutes regarding medical practice or other health practice professions acts, definitions and/or scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations, and rules for Medicare payment for GIP panels utilizing multiplex NAATs and must properly submit only valid claims. The medical necessity provisions in this LCD must be applied within the context of the manual rules. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site.

Internet Only Manual (IOM) Citations:

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*,
    - Chapter 15, Section 80.1 Clinical Laboratory Services and Section 80.6 Requirements for Ordering and Following Orders for Diagnostic Tests
- CMS IOM Publication 100-04, *Medicare Claims Processing Manual*,
    - Chapter 16, Laboratory Services
- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*,
    - Chapter 13, Section 13.5.4 Reasonable and Necessary Provision in an LCD

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment may be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.

Code of Federal Regulations (CFR) References:

- CFR, Title 42, Volume 2, Chapter IV, Part 410.32, Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.
- CFR, Title 42, Volume 2, Chapter IV, Part 411.15(a), Particular services excluded from coverage.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Compliance with the provisions in this LCD may be monitored and addressed through post payment data analysis and subsequent medical review audits.

For many gastrointestinal infections, particularly noninflammatory diarrhea and acute gastroenteritis of short duration, no laboratory testing is recommended.[1] In the past, diagnostic testing for these pathogens was accomplished by techniques such as stool culture or examination for ova and parasites. Multiplex nucleic acid-based assays are now available to detect a number of these pathogens in a single stool sample, with results available in a much shorter timeframe. Diagnostic tests may be medically reasonable and necessary according to Medicare when they affect patient management to improve health outcomes.

This LCD provides limited coverage for outpatient testing of GIP panels utilizing multiplex nucleic acid amplification techniques (NAATs) for specific conditions. This LCD does not address coverage in the inpatient setting.

History/Background and/or General Information

The Centers for Disease Control estimates that illness potentially transmitted through food causes roughly one in six Americans (or 48 million people) to become sick, 128,000 people to be hospitalized, and 3,000 deaths each year.[2] Infectious diarrhea may be due to a variety of pathogens including bacteria, parasites, and viruses.[2-5] Conventional diagnostic testing for these pathogens includes techniques such as stool culture or examination for ova and parasites. Historically, treatment decisions were based on symptoms or conventional diagnostic test results. More recently, multiplex nucleic acid-based assays have been introduced to detect a number of pathogens in a single sample, and most require less time than conventional testing methods.[1,6-8]

Recent development of commercial, panel-based, molecular diagnostics for the rapid detection of certain pathogens has resulted in a shift in clinical microbiology and clinical practice.[6] These panel-based assays offer less time for sample preparation, rapid turnaround time, and detection of a large number of microorganisms. The tests present challenges including definition of ideal test utilization strategies (e.g., optimal ordering) and test interpretation. Clinicians may not be familiar with all organisms and/or resistant genes that are detected, which may lead to inappropriate treatment and unnecessary subsequent laboratory testing. The design of the multiplex platforms, including those marketed as closed systems, carries a risk of contamination which may be difficult to recognize.[6] Studies demonstrate that, compared to conventional methods, the use of multiplex panels increase the positivity rates of GI pathogens by two to four fold.[9] Thus, another challenge is with the broad use of multiplex GIP panels, how will healthcare providers use and interpret the large amount of data made available.[9]

The literature supports that the use of GIP panels for the detection of specific pathogens associated with gastrointestinal disease may be important in certain patient populations, such as immunocompromised hosts, the critically ill, or individuals with prolonged disease that is refractory to treatment.[1,8,10]

Diarrhea:

One of the most commonly reported illnesses in the United States is acute diarrhea. For the purposes of this LCD,

acute diarrhea is defined as lasting less than 14 days, persistent diarrhea is defined as lasting between 14 and 30 days, and chronic diarrhea is defined as lasting longer than 30 days.[5] Severe illness is defined as total disability due to diarrhea, moderate illness is defined as the ability to function but with forced change in activities, and mild illness is defined as no change in activities. The best specimen is a diarrheal stool sample which is characterized as a sample that will take the shape of the container.[1,10]

Clostridium difficile (C. difficile):

The diagnosis of *C. difficile* infection is based on a combination of laboratory and clinical findings including: (a) the presence of diarrhea or evidence of megacolon or severe ileus, and (b) either a positive laboratory test result or evidence of pseudomembranes on endoscopy or histopathology. *C. difficile* is the most commonly recognized cause of infectious diarrhea in healthcare settings. Advanced age and duration of hospitalization are two of the most important risk factors for *C. difficile* infections. The most important modifiable risk factor is exposure to antibiotics.[11]

C. difficile is a spore-forming, anaerobic, gram-positive bacillus that is picked up from the environment or via the fecal-oral route. The presence of *C. difficile* Toxins A and B are responsible for gastrointestinal disease.[12] Toxin or nucleic acid amplification testing for *C. difficile* should only be done on diarrheal stool, not formed stools, unless the physician notes that the patient has an ileus.[1]

Travelers' diarrhea (TD):

Gastrointestinal problems remain the first complaint among travelers with health problems.[13] TD is defined as a gastrointestinal infection resulting in loose, watery stools that occur during travel or within ten days of returning from travel to resource-limited countries or regions. TD can be classified as functional impact: mild, moderate or severe based on the number of loose stools that are passed in 24 hours. The overall impact of TD is substantial although declining due to awareness and improvements of global health, sanitation and hygiene.[14]

Unless treatment is indicated, diagnostic testing is not recommended in most cases of uncomplicated TD.[10] Travelers with diarrhea lasting 14 days or longer should be evaluated for intestinal parasitic infections (strength of recommendation: strong, quality of evidence: moderate).[10] In addition, the guidelines from the Infectious Disease Society of America recommend that gastrointestinal tract disease including inflammatory bowel disease and postinfectious irritable bowel syndrome (IBS) should be considered during evaluation.[10] Testing for *C. difficile* should be performed in travelers treated with antimicrobial agent(s) within the preceding eight to 12 weeks.[10]

The Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report,[14] also support microbiologic testing in returning travelers with severe or persistent symptoms (diarrhea lasting two weeks or longer) or in those who fail empiric therapy. The authors also state that molecular testing, aimed at a broad range of clinically relevant pathogens, is preferred when rapid results are necessary for a direct medical treatment decision, or when non-molecular tests available have failed to establish a diagnosis (ungraded).[14] The authors noted no studies have been published which show that using molecular testing improves patient outcomes.[14]

Covered Indications

1. GIP panels utilizing NAATs, 11 or fewer targets, are medically reasonable and necessary for the evaluation of Medicare beneficiaries with the following:

    - Acute diarrhea present for at least seven days duration[1, 5, 10]; **or**
    - Persistent diarrhea of 14-30 days[1, 5, 10]; **or**
    - Acute diarrhea with signs or risk factors for severe disease to include any of the following:
        - fever,

- bloody diarrhea,
- dysentery,
- dehydration,
- severe abdominal pain,
- hospitalization, or
- an immunocompromised state [1, 5, 10]

2. GIP panels utilizing NAATs, 12 or more targets, are medically reasonable and necessary for the evaluation of Medicare beneficiaries with the following:

    - An immunocompromising medical condition with acute or persistent diarrhea.[1,9,10]

Limitations

GIP panels utilizing multiplex NAATs are considered not medically reasonable and necessary for any of the following:

1. Using a single NAAT or multiplex NAAT to test for clearance of the pathogen (i.e., "test of cure").[1, 11]
2. Testing of asymptomatic patients.[1,6,10,11,15]
3. Repeat testing utilizing the same or a different GIP panel within seven days during the same episode of diarrhea by the same or different provider.[1,11]
4. Performance of more than one GIP panel on the same date of service by the same or different provider.

It is expected that GIP panels utilizing multiplex NAATs for the evaluation of chronic diarrhea (e.g., infectious) would be rare,[5, 10] and may be considered for coverage on redetermination.

Provider Qualifications

Laboratory services must meet all applicable requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), as set forth at 42 CFR part 493. Please see CMS IOM, Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.1 – Laboratory services, for provider applicable requirements.

Notice: Services performed for any given diagnosis must meet all of the indications and limitations stated in this LCD, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.

Summary of Evidence

A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Disease Society of America and the American Society of Microbiology[1] includes guidance for infections of the gastrointestinal tract. The guide states for many gastrointestinal infections, particularly noninflammatory diarrhea and acute gastroenteritis of short duration, no laboratory testing is recommended. The specimen of choice to diagnose diarrheal illness is diarrheal stool, not a formed stool or a swab, except in pediatrics where a swab is acceptable when feces are noted on the swab. Multiple stool specimens are rarely indicated for the detection of stool pathogens. Toxin or nucleic acid amplification testing for *C. difficile* should only be performed on diarrheal stool unless the patient has a confirmed diagnosis of ileus.[1]

The guide states the appropriate approach to the diagnosis of diarrheal illness is determined by the patient's age and status, severity of the disease, duration and type of illness, time of year, and geographic location. For severe, bloody, febrile, dysenteric, nosocomial, or persistent diarrhea, fecal testing using culture or culture-independent methods is indicated. To determine what organisms, methods, and screening parameters are included as part of the routine culture or culture-independent method, communication with the laboratory is required. Stool cultures often fail to detect the causative agent; therefore when necessary, culture-independent methods are recommended as adjunct methods.[1]

Culture-independent methods can detect pathogens in one to five hours compared to 24 to 96 hours required for cultures. The assays are reported to be more sensitive than culture and have much higher detection rates. Highly multiplexed assays allow for the detection of mixed infections. The importance of detection of each pathogen is unclear. The clinical significance of a greater number of pathogens detected by the more sensitive assay is uncertain, and could confound treatment. Culture-independent methods should not be used as a test of cure, because they will detect both viable and nonviable organisms.[1,11]

C. difficile toxin detection by either enzyme immunoassay (EIA) or immunochromatographic methods are widely used in clinical practice. These tests have a reported sensitivity of 70%-85% with faster result time than the toxigenic culture and the cytotoxin assay. Glutamine dehydrogenase antigen assays are sensitive but not specific. NAATs for the detection of *C. difficile* have a reported sensitivity of 93%-100%.[1] NAATs detect viable and nonviable organisms; therefore, to reduce the identification of colonized patients, some laboratories are performing both NAATs and toxin production tests. When testing is limited to patients with unexplained and new-onset diarrhea who are not receiving laxatives, NAAT alone or toxin EIA as part of a multistep algorithm are recommended.

Historically, it has been recommended that three specimens collected over a seven-to-ten-day period be submitted for ova and parasite (O&P) examination. Options today include O&P examination of a second or third specimen if the previous was negative and the patient remains symptomatic. Targeted use of immunoassay testing or NAAT for the most common parasites based on geographic location, patient demographics, and physician request can be used as a screen, only for negative patients with continued symptoms or for patients with specific risk factors requiring full O&P examination. Immunoassays for Giardia are sensitive enough that only one specimen may be needed. No data is currently available on the number of specimens required to rule out infection via NAAT. Pathogenic *Entamoeba histolytica* can only be differentiated from nonpathogenic *Entamoeba dispar* using an immunoassay or NAAT.[1]

Viral gastroenteritis is often of short duration and self-limited, and viral shedding may persist after resolution of symptoms. Testing via multiplex NAATs is not routinely performed except in immunocompromised patients, for infection control purposes, or for outbreak investigations. Testing for cytomegalovirus in immunocompromised patients should be performed using a quantitative NAAT performed on plasma.[1]

The Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)[11] states their recommendations are intended to optimize patient care based on a systematic review of the evidence and an assessment of the benefits and harms of alternative care options. Per the guideline, repeat testing (within seven days) during the same episode of diarrhea is not recommended. Also, stool testing from asymptomatic patients is not recommended, except for the purpose of epidemiological studies (strong recommendation, moderate quality of evidence).[11]

The American College of Gastroenterology (ACG) Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults[5] focuses primarily on immune-competent adult individuals and does not consider *C. difficile* associated infections. For epidemiology and public health considerations, diagnostic evaluation using stool culture and culture-independent methods, if available, should be used when the individual patient is at high risk for

spreading the disease and during known or suspected outbreaks. The recommendations for diagnosis include use of stool diagnostic studies, if available, in cases of dysentery, moderate-to-severe disease, and symptoms lasting greater than seven days in order to clarify the etiology of the illness and enable specific directed therapy. For the majority of cases of acute diarrheal illness, traditional methods of diagnosis fail to identify the etiology. 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. Antibiotic sensitivity testing for management of acute diarrheal infections is not recommended.

While not considered in the ACG guidelines[5], the work-up for chronic diarrhea is briefly discussed and recommended to include the differential diagnoses such as celiac disease, Crohn's disease, eosinophilic gastroenteritis, and Whipple's disease. In the situation of chronic diarrhea occurring after infectious diarrhea, a diagnosis of postinfectious IBS must be considered.[10] The likely pathogens in cases of infectious chronic diarrhea are the parasites *Cryptosporidium spp*, *Giardia lamblia*, *Cyclospora cayetanensis*, *Cystoisospora belli*, and *Entamoeba histolytica*.[10]

The 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea[10] recommend a detailed clinical and exposure history be obtained from patients with diarrhea under any circumstance with adherence to jurisdictional recommendations for outbreak reporting and infection control. Patients with fever or bloody diarrhea should be evaluated for enteropathogens for which antimicrobial agents may provide clinical benefit. Enteric fever should be considered in a febrile patient with exposure to *Salmonella enterica* subspecies *Typhi* or *Paratyphi*. When a possible Shiga toxin-producing organism is suggested by clinical or epidemic history, diagnostic approaches should be applied that detect Shiga toxin and distinguish *Escherichia coli* (*E. coli*) O157:H7 from other Shiga toxin-producing *E. coli* (STEC) in stool. Diagnostic tests that can distinguish between the more potent Shiga toxin 2 and less potent Shiga toxin 1 could be used. *Shigella dysenteriae* type 1, and rarely other pathogens, may produce Shiga toxin and should be considered as a cause of hemolytic-uremic syndrome (HUS), especially in patients with a recent history of international travel or personal contact with a traveler. Clinicians should evaluate for postinfectious and extraintestinal manifestations of enteric infections.

Stool testing should be performed to detect *Salmonella, Shigella, Campylobacter, Yersinia, C. difficile*, and STEC in patients with diarrhea who also have fever, bloody or mucoid stools, severe abdominal cramping or tenderness, or signs of sepsis. Bloody stools are not expected with *C. difficile* infections. STEC O157 should be assessed by culture and non-O157 STEC should be detected by Shiga toxin or genomic assays. Specifically, test for *Yersinia enterocolitica* in patients with persistent abdominal pain and fever at epidemiologic risk for yersiniosis. Stool specimens should be tested for Vibrio species in patients with large volume rice water stools or exposure to either salty or brackish waters, who have consumed raw or undercooked shellfish, or who have traveled to cholera-endemic regions within three days prior to onset of diarrhea. A broader set of bacterial, viral, and parasitic agents should be considered in the context of a possible outbreak of diarrheal illness. Selection of agents for testing should be based on a combination of host and epidemiologic risk factors and ideally in coordination with public health authorities.[10]

For immunocompromised patients with diarrhea, a broad differential diagnosis is recommended for evaluation of stool specimens by culture, viral studies and examination for parasites. Patients with acquired immune deficiency syndrome and persistent diarrhea should undergo testing for additional organisms including, but not limited to, *Cryptosporidium, Cyclospora, Cystoisospora*, microsporidia, *Mycobacterium avium* complex, and CMV.[10]

Clinical consideration should be included in the interpretation of multiplex NAAT because these assays detect deoxyribonucleic acid (DNA) and not necessarily viable organisms. All specimens that test positive for bacterial pathogens by culture-independent diagnostic testing such as antigen-based molecular assays (gastrointestinal tract panels), and where isolate submission is requested or required under public health reporting rules, should also be cultured in the clinical laboratory or at a public health laboratory to ensure that outbreaks of similar organisms are detected and investigated. A culture may also be required when antimicrobial susceptibility testing results would affect care or public health responses. Specimens from patients involved in an outbreak should be tested per public health department guidance.[10]

In cases of outbreak when there is clinical suspicion of enteric fever or diarrhea with bacteremia, it is recommended that culture independent testing, including molecular diagnostics, should be performed on stool and blood specimens.[10]

Testing may be considered for *C. difficile* in patients older than two years of age, with a history of diarrhea following antimicrobial use, or in patients with healthcare associated diarrhea. A single diarrheal stool specimen is recommended for detection of toxin or a toxigenic *C. difficile* strain.[10]

A diarrheal stool specimen is optimal for laboratory diagnosis of infectious diarrhea. A fresh stool sample is preferred for the identification of viral agents, protozoal agents, and *C. difficile* toxin. Molecular techniques generally are more sensitive and less dependent on the quality of the specimen than culture. Follow-up testing is not recommended in most patients following resolution of diarrhea. Collection and analysis of serial stool specimens using culture-dependent methods are recommended by local health authorities in certain situations.[10]

The Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report[14] indicates concerns regarding molecular testing and the detection of colonization rather than infection as well as the use of molecular diagnostic methods that do not allow for characterization of microbial resistance to antibiotics. Thus, the clinician may be in a position of ordering both culture-based and molecular tests to fully evaluate the patient's illness and identify the best therapy. Further studies are needed to evaluate the utility of these assays in a clinical setting of the returning traveler with diarrhea.

Per the article, New molecular diagnostic tools in traveler's diarrhea, the increase in worldwide tourism has led to an increase in imported diseases in patients returning to their home countries.[13] Gastrointestinal problems remain the first complaint among travelers with health problems. Although most episodes of acute TD may resolve without the need for antimicrobial treatment and without identification of the causative agent(s), antibiotic treatment reduces the duration of diarrhea and related symptoms and also decreases time spent incapacitated. Bloody diarrhea and persistent diarrhea always require further investigation.[13] Early diagnosis allows an appropriate antibiotic prescription, if needed, and helps to decrease unnecessary prescriptions. Antibiotic treatment can increase the risk of HUS in cases of STEC; therefore, rapid detection can have a significant impact on patient outcome through informing clinical decisions. An additional advantage of rapid diagnosis is the potential to improve public health response during outbreaks.

Molecular techniques for the routine diagnosis of diarrhea have been widely introduced in microbiological laboratories worldwide. An important advantage to multiplex testing is the automation of the laboratory workflow. Additional advantages include speed, less need for highly specialized technical personnel, minimal handling time, and reduced risk of contamination. Previous studies have shown the sensitivity of molecular assays is higher than culture and microscopy-based methods.[5] Two of the main limitations of multiplex testing are an inability to distinguish between infection and colonization and the detection of an insignificant pathogen load that might not be involved with a patient's clinical circumstances.[6, 13] All microbiological results should be interpreted within a clinical context.[13] While multiplex testing can detect lower levels of pathogenic organisms, false positive results can arise from detection of nonviable microorganisms, free DNA or RNA, or nonspecific amplifications.[13] In addition, multiplex testing does not require culturing of live organisms, which can limit downstream organism typing studies required for outbreak assessments. Limitations in the detection of antibiotic resistance can be another pitfall in utilizing multiplex tests.[13] Finally, the fixed composition of the majority of the molecular panels commercially available can limit the utility of these tests in less common disease presentations and contexts.[13] There is a need for open multiplex molecular platforms where the consumer can combine different pathogens to be detected based on the local epidemiology, patient characteristics, and origin of the diarrhea.[13]

The health technology assessment of multiplex tests identifying gastrointestinal bacteria, viruses and parasites in

patients with suspected infectious gastroenteritis[16] concluded that in general, multiplex testing correctly identifies pathogens that are also identified by conventional testing. However, multiplex tests can also generate additional positive results not seen in conventional testing, which have uncertain clinical significance and potential to delay the patient's ability to return to their job. Positive results could lead to unnecessary treatment when presenting symptoms would spontaneously resolve with watchful waiting. Negative results could lead to premature discharge from the hospital.

Multiple studies[3,4,15-21] evaluated the FilmArray GIP panel. In most of the studies, the FilmArray specimens were submitted in Cary-Blair enteric transport medium and a few studies used frozen specimens. The studies used several different versions of the test, including a version for investigational use only, version 1.7, and version 2.0. The FilmArray GIP panel consists of automated nucleic acid extraction, reverse transcription, amplification, and analysis with results available in approximately one hour. The test detects 22 agents, including bacteria, viruses, and parasites. The studies compared the results of the multiplex panel with conventional laboratory techniques.

In all of the studies,[3,4,15-21] the FilmArray GIP panel was positive for more pathogens than the conventional laboratory techniques and detected multiple pathogens in a single specimen at a higher rate than the conventional laboratory techniques. Limitations to the studies included a low number of positive specimens for some of the test targets, a lack of differentiation between live and dead organisms in FilmArray results, detection by FilmArray of organisms at non-pathogenic levels, unclear significance to clinical implications of detected coinfections, lack of clear distinction between detection of symptom-associated organisms versus asymptomatic shedding of organisms (colonization), and inability to untangle the influences and biases inherent to differences in geographic locations, seasons of sampling, and varied patient populations.

In the Buss et al[3] clinical trial, the FilmArray GIP panel had 100% sensitivity/positive agreement (PPA) for 12 of the 22 targets and had greater than or equal to 94.5% sensitivity/PPA for an additional seven of 22 targets. It was not possible to assess the sensitivity/PPA for *Vibrio* spp., *Vibrio cholerae*, and *Entamoeba histolytica*, as the organisms were not detected by comparator methods, or at all in the case of *Entamoeba histolytica*. The specificity/negative percent agreement (NPA) was greater than or equal to 97.1% for all targets. In the Piralla et al[17] trial, the PPA was 87.5% and the NPA was 77.1%.

In the Beal et al[15] trial, researchers assessed the impact of the FilmArray GIP panel. The study found patients who had multiplex panel testing had fewer additional stool tests, fewer imaging studies, and fewer days on antibiotics. The overall length of stay was decreased by 0.5 days. Limitations of the study included absence of confirmatory testing when the results of multiplex panel tests and the conventional tests did not agree and the use of a historical cohort of patients for the control group as opposed to a contemporary group of patients alongside the test group.

In the Cybulski et al[19] trial, the clinical impact of the FilmArray GIP panel was assessed. The investigators found patients with infections detected by the multiplex panel test were more likely to receive targeted rather than empirical therapy. Reduced time to treatment and an impact on antibiotic prescribing were also observed in STEC infections. Patients infected with pathogens identified both by culture and the multiplex panel test (concordant) tended to have greater symptom severity than those patients with positive multiplex panel tests and negative cultures (discordant). The investigators stated these observations were consistent with a higher organism burden required for positive cultures and the relationship of disease severity to the level of organism burden. Patients with coinfections were generally younger and were more likely to have recent international travel. Limitations to the study included an insufficient size of certain subgroups to draw definitive conclusions, a retrospective medical record review methodology that was subject to confounding factors and biases, and restriction of the study to only two hospitals within a single healthcare system.

The Khare et al[8] trial compared two commercial multiplex panels for detection of gastrointestinal pathogens.

Conventional laboratory techniques, testing on the FilmArray platform, and testing on the MagPix platform (xTag gastrointestinal pathogens panel) were performed on each specimen. The investigators followed the manufacturer's instructions for the FilmArray platform; however, they modified the manufacturer's FDA cleared protocol for the xTag panel by using Cary-Blair stool instead of raw stool. The investigators found that the majority of the targets represented on the panels showed high sensitivity and specificity; however, there were analytes on both panels that showed poorer performance. The FilmArray *Aeromonas* assay had low sensitivity and the xTag assay for *Yersinia enterocolitica* had low sensitivity. The xTag assay for norovirus had low specificity. This study also found a high percentage of stool samples positive for two or more pathogens. Limitations of the study included: different volumes of stool tested by the FilmArray assay (200 microliters) and the xTag assay (100 microliters), more dilute Cary-Blair specimens performed in the xTag sample rather than the FDA cleared raw stool, a lack of available clinical information and treatment decisions to compare with the test results, a relatively low number of positive results for some targeted organisms and an absence of positive results for other targets, and the lack of confirmation for some pathogens identified in the multiplex assays due to inadequate specimen remaining for confirmatory testing and/or unavailability of confirmatory testing.

Multiple studies[6,9,22] compared Verigene, FilmArray, and xTag assays. Huang et al[22] found that each of the assays demonstrated good clinical performance in their patient population. The Verigene and FilmArray assays provided rapid, on-demand testing for individual specimens in a moderate complexity environment. The xTag assay was higher complexity but allowed greater throughput in a single batch.

The Ramanan et al[6] study found that in addition to broad coverage and the ability to identify a higher rate of coinfections, the multiplex panels offered reduced turnaround time. The authors supported that clinical laboratories need to be actively involved in the development of test utilization strategies focusing on the use and interpretation of the results of the tests as each of the panels had unique advantages and limitations. Conventional methods are still needed to detect pathogens not covered by the panels and provide antimicrobial susceptibility information.

The Binnicker[9] study noted challenges associated with interpretation of the results of the multiplex panels. First, the multiplex panels target microbial nucleic acid and cannot distinguish between viable, replicating organisms responsible for disease and nonviable pathogens or remnant nucleic acid. The second challenge identified was the use of multiplex panels may increase the detection of *C. difficile* and potentially impact isolation and treatment decisions. The third challenge relates to how health care providers will use and interpret the large amount of data that will be made available with the broad implementation of the multiplex panels. In the conclusions, the author found each of the multiplex panels had unique advantages and limitations that a clinical microbiology lab must consider. Although the panels increased both the positivity rate and the number of coinfections detected, cultures will continue to be needed for antibiotic susceptibility and epidemiologic investigations. Future studies need to address clinically related issues, including the impact of the panels on antibiotic use and the influence the results have on management decisions and patient outcomes. In the author's opinion, reserving the highly multiplexed panels to immunocompromised patients, the critically ill, or patients with prolonged diarrhea may improve test utilization and reduce inappropriate antibiotic use.

Summary of Evidence (Post Comment Period)

In the Axelrad et al [23] retrospective study, resource utilization was compared between patients receiving conventional stool testing (stool cultures with or without an ova and parasites exam or enzyme immunoassay for viral pathogens) and patients receiving GI panel testing (FilmArray GI pathogen panel). Both populations were from the same site (New York Presbyterian-Columbia University Medical Center), but were tested during two different time frames: conventional testing between 2012-2015 and GI panel testing between 2015-2017. Both outpatient and inpatient populations were included. Outcome metrics included the post-test likelihood to undergo endoscopy, to receive abdominal radiology, to be prescribed an antibiotic, to require a longer hospital stay, and to require a follow-up emergency department visit. Overall, the absolute risk of receiving endoscopy, abdominal radiology, and antibiotics was found to be lower in the GI panel testing population. This finding was thought to be associated with a

higher rate of positive test results in the GI panel population. The researchers disclosed several limitations to their study including incomplete information on patient presentation and outcome and lack of thorough investigation into the cause and effect of positive findings and the patient's signs and symptoms. Additionally, it should be noted that no significant discussion differentiating results and outcomes between outpatients and inpatients was identified while reviewing this publication.

In the Chang et al [24] meta-analysis, two different Polymerase Chain Reaction (PCR) multiplex-based tests (Luminex xTAG GPP and FilmArray GI panel) were compared across 11 studies and conclusions were drawn regarding the accuracy of both tests as compared to gold standards and regarding the performance of these two tests as compared to each other. The researchers concluded that both tests were "highly accurate" with FilmArray demonstrating overall "higher sensitivity and post-test probability" than xTAG GPP. However, the researchers stated that the meta-analysis did not clarify how these results would "translate to a clinical setting."

In the Machiels et al [25] study, patients at the Rodboud University Medical Center were evaluated using "routinely performed" PCR panels. In parallel, the same specimens were evaluated by the FilmArray GI panel, but these results were not used to guide patient care. Then, the patients' clinical courses were analyzed retrospectively, and the researchers theorized alternate clinical outcomes for these patients had the FilmArray GI panel been used instead of the PCR panels. The FilmArray GI panel was predicted to improve patient care. This prediction was extrapolated through comparing the number of pathogens detected by and the turn-around times of each test. Of note, the researchers stated "In the outpatient population, we found no impact on either antibiotic therapy or the number of prevented diagnostic procedures (data not shown)."[25]

Contractor Advisory Committee (CAC) Evidentiary Summary

After review of literature, the CAC advisory panel, which met in April of 2019, discussed GIP panels utilizing NAATs. In general, the biggest difference between the GIP multiplex NAAT testing panels is the number of targets. Viruses can shed even in asymptomatic patients and an issue with the multiplex NAATs testing panels is false positive results. The CAC panel emphasized history and physical are important as well as severity and duration of the patient's symptoms in determining which test should be performed. The CAC panel mentioned overuse is always a concern with new tests and recommended these tests not be done routinely or at first encounter in an emergency department stating there should be criteria set such as fever, diarrhea, or bloody stools. The CAC panel considered the guidelines and noted differences between the current ACG and IDSA guideline recommendations. The CAC panel discussed that the GIP multiplex NAAT testing panels are not to be ordered on the otherwise healthy patient stating these tests are more appropriate for the patient who is already ill, such as transplant patients or immunosuppressed patients, when the provider needs specific information quickly.

Analysis of Evidence (Rationale for Determination)

In all of the studies evaluating sensitivity and specificity of the GIP panels utilizing multiplex NAATs, stool specimens were tested. The use of GIP panels utilizing multiplex NAATs on specimens other than stool has not been evaluated for sensitivity and specificity. The literature reviewed supports the appropriate approach to the evaluation of diarrheal illness is determined by the patient's age and status, severity of the disease, duration and type of illness, time of year, and geographic location.[1] A detailed clinical and exposure history should be obtained from all patients with diarrhea. For many gastrointestinal infections, particularly noninflammatory diarrhea and acute gastroenteritis of short duration, no laboratory testing is recommended.[5] For severe, bloody, febrile, dysenteric, nosocomial, or prolonged acute diarrhea, fecal testing is indicated.[1] The five most common bacterial gastrointestinal pathogens causing bloody diarrhea are Salmonella, *Shigella, Campylobacter, Yersinia*, and STEC.

Since publication of guidelines by the American Society for Microbiology on utilization of optimal tests for detection of pathogens, several gastrointestinal panels that detect more than 20 viral, bacterial, and parasitic enteric organisms have become available.[10] The guidelines focus on clinical presentation of acute and persistent diarrhea, particularly in the United States; therefore, this LCD provides limited coverage for outpatient GIP testing with panels of 11 or

fewer pathogens for beneficiaries with acute diarrhea lasting at least seven days, for persistent diarrhea, and for beneficiaries with acute diarrhea with signs or risk factors for severe disease.[1, 5, 10]

For immunocompromised beneficiaries with acute or persistent diarrhea, a broad differential diagnosis is recommended for evaluation of stool specimens by culture, viral studies and examination for parasites (strong recommendation, moderate quality of evidence);[10] therefore, this LCD provides limited coverage of outpatient GIP testing with panels of 12 or more pathogens.[1, 9, 10]

GIP testing for likely pathogens for beneficiaries with chronic diarrhea, defined as lasting longer than 30 days,[5] is limited to rare instances. The 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea[10] supports testing for the likely pathogens *Cryptosporidium spp, Giardia lamblia, Cyclospora cayetanensis, Cystoisospora belli*, and *Entamoeba histolytica* in patients with persistent or chronic diarrhea (strong recommendation, moderate quality of evidence). According to the ACG Clinical Guideline, [5] performance of a thorough and directed history is essential as the history may direct further investigations when evaluating persisting symptoms.

Testing may be considered for *C. difficile* in patients age two years old or greater who have a history of diarrhea following antimicrobial use and in patients with healthcare associated diarrhea.[10] The use of multiplex panels may increase the detection of *C. difficile* and potentially impact isolation and treatment decisions.[9] Singleplex NAAT for *C. difficile* toxin genes are available.

Unless treatment is indicated, diagnostic testing is not recommended in most cases of uncomplicated TD.[1] Travelers with diarrhea lasting 14 days or longer should be evaluated for intestinal parasitic infections. Testing for *C. difficile* should be performed in travelers treated with antimicrobial agent(s) within the preceding twelve weeks (strong recommendation, moderate quality of evidence).[10]

Selection of agents for testing should be based on a combination of host and epidemiologic risk factors. Clinical consideration should be included in the interpretation of multiplex NAATs because these assays detect DNA/RNA and not necessarily viable organisms, or they may detect an insignificant pathogen load that might not be the cause of the diarrhea. Since NAATs detect viable and nonviable organisms, this LCD limits testing to symptomatic beneficiaries (strong recommendation, low/moderate quality of evidence).[1,6,10,11,16] Follow-up testing is not recommended in most people following resolution of diarrhea (strong recommendation, moderate quality of evidence);[10] therefore, this LCD does not provide coverage of testing for clearance of the pathogen ("test of cure") and for repeat testing with GIP Panels utilizing NAATs within seven days during the same episode of diarrhea.[1,11]

Analysis of Evidence (Post Comment Period)

The literature submitted during the comment period reinforces the usefulness of GIP panels. However, the articles do not clearly establish a minimum or maximum number of targets best suited for evaluation of patients in various clinical scenarios; instead, the studies utilized panels with established sizes (e.g., a 22 pathogen panel) and either compared these panels to standard of care (e.g., stool cultures) or other molecular tests, including different panels. Additionally, please note that the LCD only addresses testing in the outpatient setting. In the literature submitted, the impact of GIP testing in the outpatient versus inpatient population was only briefly examined. One study stated, "In the outpatient population, we found no impact on either antibiotic therapy or the number of prevented diagnostic procedures (data not shown)."[25] Medicare only provides coverage for medically reasonable and necessary testing; thus, testing should be tailored to specific clinical circumstances and only ordered when it is expected to have an impact on clinical management of the patient. While large GIP panels may be able to encompass a broad differential diagnosis, often preliminary findings (e.g., history and physical) can rule out several potential etiologies, eliminating the need for indiscriminate testing.

General Information

Associated Information

Please refer to the related Local Coverage Article: Billing and Coding: Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs), A56638 for documentation requirements, utilization parameters and all coding information as applicable.

Sources of Information

Other Contractors' Policies
Palmetto GBA, L37709 Foodborne Gastrointestinal Panels Identified by Multiplex Nucleic Acid Amplification (NAATs)
Contractor Medical Directors

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
10/16/2022	R1	LCD posted for notice on 09/01/2022 to become effective 10/16/2022. Proposed LCD posted for comment on 4/14/2022.	• Creation of Uniform LCDs With Other MAC Jurisdiction

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A56638 - Billing and Coding: Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs)

A59195 - Response to Comments: Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs)

LCDs

DL38227 - Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs)

Related National Coverage Documents

N/A

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