Test Specific Guidelines

Molecular Gastrointestinal Pathogen Panel (GIPP) Testing

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Introduction

Molecular gastrointestinal pathogen panel testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Gastrointestinal Pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, Norovirus, Giardia), Includes Multiple Reverse Transcription, When Performed, And Multiplex Amplified Probe Technique, Multiple Types Or Subtypes, 3-5 Targets	87505
Gastrointestinal Pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, Norovirus, Giardia), Includes Multiple Reverse Transcription, When Performed, And Multiplex Amplified Probe Technique, Multiple Types Or Subtypes, 6-11 Targets	87506
Gastrointestinal Pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, Norovirus, Giardia), Includes Multiple Reverse Transcription, When Performed, And Multiplex Amplified Probe Technique, Multiple Types Or Subtypes, 12-25 Targets	87507

What Are Nucleic Acid Amplified Probe Techniques (NAAT) for the Identification of Microorganisms via GIPP?

Definition

Tests performed by NAAT use a microorganism's DNA or RNA to directly identify

specific bacteria, viruses, and/or protozoa rather than standard microorganism detection techniques such as bacterial culture, microscopy with and without stains, direct fluorescent antibody testing, rapid antigen testing, qualitative and quantitative immunoassay for identification of antigens or toxins from stool and single-plex PCR assays. Multiplex NAAT tests are included in the larger grouping of culture-independent diagnostic tests (CIDT). CIDT includes, but is not limited to, simplex direct probe and amplified probe techniques.

This technology offers results in a matter of hours, rather than 2-3 days of time-consuming and labor intensive bacterial cultures and immunoassays for processing stool specimens. CIDT are touted as providing a more comprehensive assessment of disease etiology by increasing the diagnostic yield compared with conventional diagnostic tests permitting earlier initiation of appropriate therapeutic agents targeted to the detected pathogen(s), if any, rather than empirical therapy until culture results are available.

However, above and beyond microorganism detection, this type of testing does not provide the culture isolates that are needed for antimicrobial susceptibility testing, serotyping, subtyping and whole genome sequencing that are critical for monitoring trends, detecting clusters of illness and investigating outbreaks.[1]

Gastrointestinal Infectious Disorders

Gastrointestinal diseases caused by pathogens are among the most common infectious disorders worldwide, with more than 300 million individuals in the US affected annually. The most common presenting symptom is diarrhea, which is self-limiting in most otherwise healthy individuals. However, if left untreated in the very young, especially in areas with poor hygiene, diarrhea can become a life threatening illness.[2]

Test Information

Introduction

Molecular testing for gastrointestinal parasites may include panels with varying numbers of microorganism targets.

In addition to CLIA-regulated laboratory developed tests (LDTs) by specialty (e.g. academic) laboratories, several commercial GIPP assays are currently available. For example, Binnicker has evaluated three FDA-cleared GIPP assays,[3] and all are closed system tests that do not allow random access for physicians to select likely etiologic agents of diarrhea.

Please note that the NAAT results of GIPP assays can be inconclusive and non-specific, such as the inability to always distinguish pathogenic from non-pathogenic organisms, or viable from nonviable organisms.[4]

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Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to GIPP testing.

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2016) Clinical Guidelines included two relevant sections pertaining to GIPP:[5]

"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)."

"The new diagnostics' best applicability is for the clinician in practice, seeing one patient at a time rather than in the public health setting, e.g., in outbreak investigations. One potential drawback of molecular technologies is the need to predefine the particular microbes being sought. In addition the significance of an identified organism may not be clear as these molecular technologies, which involve nucleic acid amplification, are limited to our existing knowledge of a microbes' genome and do not discriminate between viable and non-viable organisms. As a result they can detect microbes at non-pathogenic levels. Given the high rates of asymptomatic carriage of enteropathogens, this can be a considerable problem. To confound matters, further multiplex techniques are more commonly associated with increased detection of mixed infections and the relative importance of each pathogen may be unclear."

An ACG (2021) guideline addressing *C. difficile* stated:[6]

"CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (conditional recommendation, low quality of evidence)."

As NAAT testing is unable to distinguish asymptomatic colonization from active infection, a multi-step testing algorithm is recommended instead of NAAT testing alone.

Infectious Disease Society of America

The Infectious Diseases Society of America (IDSA, 2017) Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea made the following recommendations:[7]

"A broad differential diagnosis is recommended in immunocompromised people with diarrhea, especially those with moderate and severe primary or secondary immune deficiencies… Some experts have proposed that these assays may be particularly well suited for making an organism-specific diagnosis in immunocompromised patients."

"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 or diarrhea with bacteremia (strong, moderate)."

"Multipathogen nucleic acid amplification tests can simultaneously detect viral, parasitic, and bacterial agents, including some pathogens that previously could not be easily detected in the clinical setting such as norovirus, and enterotoxigenic E. coli (ETEC), enteropathogenic E. coli (EPEC), and enteroaggregative E. coli (EAEC) in less time than traditional methods. The short time to results could reduce inappropriate use of antimicrobial agents to treat infections that do not require antimicrobial therapy and could shorten the time to targeted management and isolation measures for certain infections such as STEC O157. With these assays, it is common to detect the presence of >1 pathogen that may differ with regard to clinical management."

"Even a positive result for 1 pathogen should be interpreted in the context of the patient's clinical presentation, because less is known about the clinical significance of tests that detect nucleic acid as compared with traditional assays that generally detect viable organisms. The importance of detection of multiple pathogens in the same specimen is often unclear; it is unknown if all pathogens detected in the specimen are clinically relevant or if one is more strongly associated with the illness."

An IDSA (2018) Clinical Practice Guideline for Laboratory Diagnosis of Infectious Diseases, Section VII. Infections of the Gastrointestinal Tract included these statements on culture-independent NAATs:[8]

"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."

IDSA acknowledges the rapid turnaround time, increasing availability, and reported high sensitivity of culture independent organism detection.

Selected Relevant Publications

Acute diarrhea, often called gastroenteritis, can be defined as the passage of a greater number of stools of decreased form from the normal lasting < 14 days. Acute diarrhea is generally associated with clinical features of nausea, vomiting, abdominal pain and cramps, bloating, flatulence, fever, passage of bloody stools, tenesmus and fecal urgency. It is the leading cause of outpatient visits,

hospitalizations, and lost quality of life occurring domestically and those traveling abroad.

Many episodes of acute diarrhea are self-limited and require fluid replacement and supportive care. Oral rehydration is indicated for patients who are mildly to moderately dehydrated. IV fluids may be required for more severe dehydration. Routine use of antidiarrheal agents is not recommended because many of these agents have potentially serious adverse effects, particularly in infants and young children. Antimicrobial therapy is typically warranted for adult and pediatric patients with immune systems which are severely weakened from medications, age and other primary/secondary immunocompromising illnesses/conditions.[8-10]

Laboratory testing algorithms for infectious causes of diarrhea generally agree that testing is NOT warranted for community-acquired diarrhea of <7 days duration without signs or symptoms of severe (fever, bloody diarrhea, dysentery, severe abdominal pain, dehydration, hospitalization and immunocompromised state) disease. In general, when community-acquired diarrhea persists for ≥7 days, or the diarrhea is travel-related, or there are signs/symptoms of severe disease, GIPP testing may be warranted. Additional directed testing may be indicated if the GIPP results are negative and diarrhea persists. No additional testing is indicated for GIPP-positive result unless the clinical pictures changes. Clostridium difficile molecular testing is warranted on health-care associated diarrhea with onset after the 3rd inpatient day or after recent antibiotic use.

Whereas a majority of microorganisms can be identified with up to 5 targets, typically including Salmonella, Campylobacter, Shigella, Cryptosporidium, and Shiga toxin producing E.coli, additional agents may be in the working differential diagnosis, such as (but not limited to) Clostridium difficile, additional E. coli variants, Yersinia enterocolitica, Vibrio parahaemolyticus, Giardia, Cryptosporidium, and viruses including norovius, rotavirus, and enteric adenoviruses.

Salient illustrations[11-13] of the literature have annotated a diverse set of offending infectious agents (bacterial, parasitic and viral) in patients presenting with acute diarrhea. However, it must be emphasized that such original study recruitment criteria were not designed to stratify probability/incidence distributions of causative organisms, according to more carefully specified patient presentation categories. Furthermore, the molecular predilection for mixed infectious agent identification is a confounding factor when clinicians are trying to pinpoint the precise etiology of acute diarrhea, given the dilemma between pathogenicity and non-pathogenicity, which was briefly cited above.

As a result, when the patient history, clinical presentation and symptoms, etc. suggest a specific microbial etiology and/or therapy, a broad GIPP consisting of >5 infectious targets is not indicated. However, broader GIPP molecular panels (e.g. 6-25 targets) might occasionally be indicated when a patient presents with a clinical scenario and overlapping symptoms consistent with multiple possible microbiological etiologies, where both diagnosis and treatment are particularly challenging (e.g., as noted above for immunocompromised patients).

Criteria

Introduction

Requests for GIPP testing are reviewed using these criteria.

The following clinical indications can support the use of molecular GIPP testing.

Individuals with acute diarrhea with moderate-to-severe symptoms (such as fever, dysentery, severe dehydration).

Individuals with community-acquired diarrhea that persists for more than seven days, or individuals with travel-associated diarrhea of uncertain etiology.

Immunocompromised individuals with acute diarrhea. Immunocompromise may support the use of a relatively large number of testing targets, in concert with other supporting clinical documentation in the medical record.

The following are contraindications to GIPP testing, with any number of targets:

Immunocompetent individuals with mild diarrhea, particularly of ≤ 7 days' duration.

Individuals in whom the clinical presentation of acute diarrhea suggests a specific infectious etiology, unless first-line laboratory testing should fail to detect the suspected organism, and there is still a high clinical suspicion of infectious etiology.

Molecular GIPP testing should not be performed as test-of-cure. Therefore, it is not medically necessary to repeat testing for the same illness.

Molecular GIPP testing is limited to the minimum number of targets needed for therapeutic decision making. When ordering any configuration of infectious disease targets, whether using GIPP or conventional culture, the medical record should clearly indicate the differential diagnosis of possible microorganisms based upon patient history and presenting signs/symptoms.

Billing and Reimbursement

If any molecular GIPP tests are billed, which have variable numbers and configurations of infectious agent targets, then the following guidelines apply to the reimbursement of CPT codes 87505, 87506, and 87507:

87505 (3-5 targets) or 87506 (6-11 targets) is supported by ICD-10-CM R19.7 (Diarrhea, unspecified), A09 (Infectious gastroenteritis and colitis, unspecified), A04.9 (Bacteria intestinal infection, unspecified), or K52.9 (Noninfective gastroenteritis and colitis, unspecified).

87507 (12-25 targets) is supported by ICD-10-CM R19.7 (Diarrhea, unspecified), A09 (Infectious gastroenteritis and colitis, unspecified), A04.9 (Bacterial intestinal infection, unspecified), or K52.9 (Noninfective gastroenteritis and colitis,

unspecified) plus at least one of the immunodeficiency-related codes in the Table: *ICD Codes Indicating Cancer, Transplant, or Other Immunocompromise*

More than one type of test for the same organism will not be reimbursable for the same date of service or within 7 days [e.g., 87493 (C. difficile detection) cannot be billed with any of the GIPP codes 87505, 87506, or 87507). In the uncommon event that the individual organism test was not included in the original GIPP panel, requests for an exception will be evaluated on a case by case basis.

No GIPP testing will be reimbursed within 7 days of another paid GIPP test, regardless of encounter or result except in the setting of immunocompromise as defined by codes in the Table: *ICD Codes Indicating Cancer, Transplant, or Other Immunocompromise*.

If the laboratory's testing platform consists solely of a multiplexed panel of 12 or more targets, yet only a subset of the organisms are considered medically necessary based on the above criteria, the lab may request reimbursement for that subset of organisms using a procedure code that does not represent all organisms included on the panel.

Exclusions and Other Considerations

Although outbreak investigations may sometimes require use of GIPP testing, the public health evaluations of such outbreaks are beyond the scope and domain of this guideline.

ICD Codes

ICD codes in this section may be used to support medical necessity as described in the above criteria.

ICD Codes Indicating Cancer, Transplant, or Other Immunocompromise

ICD code or range	Description
B20	Human immunodeficiency virus [HIV] disease
B59	Pneumocystosis
C00.X-C96.X	Malignant neoplasms
D37.X-D48.X	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
D60.X-D64.X	Aplastic and other anemias and other bone marrow failure syndromes
D70.X-D77	Other disorders of blood and blood-forming organs
D80.X-D89.X	Certain disorders involving the immune mechanism
E40-E46	Malnutrition
I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease

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ICD code or range	Description
I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
K91.2	Postsurgical malabsorption, not elsewhere classified
M35.9	Systemic involvement of connective tissue, unspecified
N18.5	Chronic kidney disease, stage 5
N18.6	End stage renal disease
T86.X	Complications of transplanted organs and tissue
Z48.2X	Encounter for aftercare following organ transplant
Z49.X	Encounter for care involving renal dialysis
Z94.X	Transplanted organ and tissue status
Z99.2	Dependence on renal dialysis

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