healthfirst
Health Insurance for New Yorkers

Reimbursement Policy

Subject:	Pathogen Panel Testing		
Policy Number:	PO-RE-012v4		
Effective Date:	02/01/2025	**Last Approval Date:**	12/16/2024

I. Policy Description

Infectious diseases can be caused by a wide range of pathogens. Conventional diagnostic methods like culture, microscopy with or without stains and immunofluorescence, and immunoassay often lack sensitivity and specificity and have long turnaround times. Panels for pathogens using multiplex amplified probe techniques and multiplex reverse transcription can detect and identify multiple pathogens in one test using a single sample (Palavecino, 2019).

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

This policy is specific to testing in the outpatient setting. Criteria below do not apply to testing allowances in situations other than the outpatient setting.

1) For individuals with persistent diarrhea or diarrhea with signs or risk factors for severe disease (i.e., fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain), multiplex PCR-based panel testing (up to **11** gastrointestinal pathogens [GIPs]) no more often than once every 7 days **MEETS COVERAGE CRITERIA**.

2) For individuals who are displaying signs and symptoms of a respiratory tract infection (i.e., temperature ≥ 102°F, pronounced dyspnea, tachypnea, tachycardia), multiplex PCR-based panel testing (up to **5** respiratory pathogens) **MEETS COVERAGE CRITERIA**.

3) Multiplex PCR-based panel testing of **12 or more** GIPs **DOES NOT MEET COVERAGE CRITERIA**.

4) Multiplex PCR-based panel testing of **6 or more** respiratory pathogens **DOES NOT MEET COVERAGE CRITERIA**.

5) Multiplex PCR-based panel testing of pathogens in cerebrospinal fluid (CSF) **DOES NOT MEET COVERAGE CRITERIA**.

6) Molecular detection-based panel testing of pathogens in the blood **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

7) Molecular detection-based panel testing of urine pathogens for the diagnosis of urinary tract infections (e.g., GENETWORx Molecular PCR UTI Test) **DOES NOT MEET COVERAGE CRITERIA**.

8) Molecular-based panel testing to screen for or diagnose wound infections (e.g., GENETWORx PCR Wound Testing) **DOES NOT MEET COVERAGE CRITERIA**.

9) Molecular-based panel testing for general screening of microorganisms (e.g., MicroGenDX qPCR+ NGS) **DOES NOT MEET COVERAGE CRITERIA**.

Scientific Background

There has been a move in recent years towards employing molecular tests that use multiplex polymerase chain reaction (PCR) to simultaneously detect multiple pathogens associated with an infectious disease rather than one organism. These tests are usually offered as a panel for a particular infectious condition, such as sepsis and blood stream infections, central nervous system infections (for example, meningitis and encephalitis), respiratory tract infections, urinary tract infections or gastrointestinal infections. These assays are often more sensitive than conventional culture-based or antigen detection. The high diagnostic yield is particularly important when clinical samples are difficult to collect or are limited in volume (e.g., CSF). Multiplex PCR assays are also particularly beneficial when different pathogens can cause the same clinical presentation, thus making it difficult to narrow down the causative pathogen. Access to comprehensive and rapid diagnostic results may lead to more effective early treatment and infection-control measures. Disadvantages of multiplex PCR assays include high cost of testing and potential false negative results due to preferential amplification of one target over another (Palavecino, 2019).

The Centers for Medicare and Medicaid Services (CMS) report that the top target pathogens causing infections include *Salmonella*, *Campylobacter*, *Shigella*, *Cryptosporidium*, Shiga toxin producing *E. coli* non-O157 and Shiga toxin producing *E. coli* O157; these pathogens "represent the top 90-95% of foodborne infections [incidence of infection per 100,000 population]" (CMS, 2022).

Proprietary Testing

Gastrointestinal Pathogen Panel

Approximately 1.7 billion cases of childhood diarrheal disease occur worldwide every year, resulting

in about 443,832 deaths in children younger than five years of age annually (WHO, 2024). The Centers for Disease Control and Prevention (CDC) has estimated that nearly 48 million cases of acute diarrheal infection occur annually in the United States, at an estimated cost upwards of $150 million (Scallan et al., 2011). Approximately 31 major pathogens acquired in the United States caused an estimated 9.4 million episodes of diarrheal illness, 55,961 hospitalizations, and 1,351 deaths each year. Additionally, unspecified agents caused approximately 38 million episodes of foodborne illnesses and resulted in 71,878 hospitalizations and 1,686 deaths. Diarrhea can be classified as acute (lasting less than 14 days), persistent (14 and 30 days), and chronic (lasting for greater than a month) (Riddle et al., 2016). Further, healthcare and antibiotic associated diarrhea are mainly caused by toxin-producing *Clostridium difficile* causing more than 300,000 cases annually (CMS, 2022).

Acute infectious gastroenteritis is generally associated with other clinical features like fever, nausea, vomiting, severe abdominal pain and cramps, flatulence, bloody stools, tenesmus, and fecal urgency. A wide spectrum of enteric pathogens can cause infectious gastroenteritis, including bacteria such as *Campylobacter, Clostridium difficile, Salmonella, Shigella, Vibrio,* and *Yersinia*; viruses, such as Norovirus, Rotavirus, Astrovirus, and Adenovirus; and parasites, such as *Giardia, Entamoeba histolytica,* and *Cryptosporidium* (Riddle et al., 2016).

Stool culture is the primary diagnostic tool for a suspected bacterial infection, but it is time-consuming and labor intensive. Stool samples are collected and analyzed for various bacteria present in the lower digestive tract via cell culture; these bacteria may be normal or pathogenic (Humphries & Linscott, 2015). By identifying the type of bacteria present in a stool sample, a physician will be able to determine if the bacteria are causing gastrointestinal problems in an individual. However, stool culture has a low positive yield. Similarly, methods like electron microscopic examination and immunoassay that are used to diagnose viruses are labor intensive and need significant expertise (Zhang et al., 2015). Multiplex PCR-based assays have shown superior sensitivity to conventional methods for detection of enteric pathogens and are increasingly used in the diagnosis of infectious gastroenteritis. These assays have significantly improved workflow and diagnostic output in the diagnosis of gastrointestinal infections (Zhang et al., 2015). Several FDA-approved multiplex PCR assays are now commercially available. Some assays can detect only bacterial pathogens in stool, whereas others can detect bacterial, viral, and parasitic pathogens. The Strong-LAMP assay is a technique which uses PCR to detect *Strongyloides stercoralis* in stool and urine samples (Fernandez-Soto et al., 2016), although it is not yet widely available (La Hoz & Morris, 2019).

Proprietary panels are available for the assessment of gastrointestinal pathogens. BioFire Diagnostics offers an FDA-approved 22-target testing panel for gastroenteritis, termed the BioFire FilmArray Gastrointestinal Panel. The panel's bacteria targets include *Campylobacter, Clostridium difficile, Plesiomonas shigelloides*, *Salmonella, Yersinia enterocolitica, Vibrio (parahaemolyticus, vulnificus,* and *cholerae),* and *Vibrio cholerae*. The panel's diarrheagenic *E. coli* and *Shigella* targets include Enteroaggregative *E. coli*, Enteropathogenic *E. coli*, Enterotoxigenic *E. coli*, Shiga-like toxin-producing *E. coli* stx1/stx2, *E. coli* O157, and *Shigella/*Enteroinvasive *E. coli*. The panel's parasite targets include *Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica,* and *Giardia lamblia*. The panel's virus targets include Adenovirus F40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, and Sapovirus (I, II, IV, and V) (BioFire, 2023b). The manufacturer claims a sensitivity of 98.5% and specificity of 99.2% for this test and states that results are available within one hour of testing. However, BioFire notes that the test has not been evaluated for immunocompromised patients (BioFire, 2023b).

The FDA-approved xTAG Gastrointestinal Pathogen Panel, developed by Luminex, can

simultaneously identify multiple bacterial, viral, and parasitic nucleic acids in both fresh and frozen human stool samples. This test can provide results in as little as five hours, and can "detect and identify >90% of the causative bacterial, viral, and parasitic agents of gastroenteritis in the same day" (Luminex, 2023b). The xTAG Gastrointestinal Pathogen Panel is able to identify *Campylobacter*, *Clostridium difficile*, Toxin A/B, *Escherichia coli* O157, Enterotoxigenic *E.coli* (ETEC) LT/ST, Shiga-like Toxin producing *E.coli* (Banerjee et al.) stx1/stx2, *Salmonella, Shigella, Vibrio cholerae, Yersinia enterocolitica,* Adenovirus 40/41, Norovirus GI/GII, Rotavirus A, *Cryptosporidium*, *Entamoeba histolytica*, and *Giardia* (Luminex, 2023b).

The Biocode Gastrointestinal Pathogen Panel is an FDA approved test that uses a 96-well microplate to simultaneously detect 17 diarrhea causing pathogens (*Campylobacter*, *Clostridium difficile* toxins A and B, *E. coli* O157, Enterotoxigenic *E. coli* LT/ST (ETEC), Enteroaggregative *E. coli* (EAEC), *Salmonella*, Shiga-like toxin producing *E. coli* stx1/stx2, *Shigella*/Enteroinvasive *E. coli*, *Vibrio*/*Vibrio parahemolyticus*, *Yersinia enterocolitica*, Adenovirus 40/41, Norovirus GI/GII, Rotavirus A, *Cryptosporidium*, *Entamoeba histolytica*, and *Giardia lamblia*) in stool samples (BioCode, 2024a). This rapid multiplex screening assay is low cost and may be helpful with infection control.

Respiratory Pathogen Panel

Upper respiratory tract infections (involving the nose, sinuses, larynx, pharynx, and large airways) can be caused by a variety of viruses and bacteria. These infections may lead to several different patient ailments such as the common cold, acute bronchitis, influenza, and respiratory distress syndromes. Regarding the common cold, the most common virus is rhinovirus; the bacteria that most commonly causes a sore throat (pharyngitis) is *Streptococcus pyogenes* (Thomas & Bomar, 2023). Lower respiratory tract infections occur in the lungs and any airways below the larynx. Lower respiratory infections include pneumonia, bronchitis, tuberculosis and bronchiolitis (Hansen et al., 2020).

Traditional methods used for the diagnosis of viral respiratory tract infections are direct antigen testing (non-immunofluorescent and immunofluorescent methods) and conventional and rapid cell culture (Ginocchio, 2007). These tests have several limitations including a slow turnaround time, low sensitivity, and labor-intensive processes. Acute respiratory infections may also be diagnosed by a simple respiratory exam, where the physician focuses on the patient's breathing and checks for fluid and inflammation in the lungs. Symptoms of a respiratory tract infection may include a stuffed nose, cough, fever, sore throat, headache, and difficulty breathing. Chest X-rays may be used to check for pneumonia, and blood/mucus samples may be used to confirm the presence of certain bacteria and/or viruses via cell culture. The doctor may also check the ears, nose, and throat. Treatment typically incorporates over the counter medications, rest, fluids, and antibiotics (if a bacterial infection is identified).

Considerable progress has been made in the development of molecular methods to detect multiple respiratory pathogens simultaneously. Molecular detection, including multiplex PCR assays, is currently the gold standard for viral respiratory diagnosis (Bonnin et al., 2016). Multiplex PCR-based assays are now commercially available to detect several viral pathogens like adenovirus, influenza A and respiratory syncytial virus as well as bacterial pathogens like *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila*. These tests are rapid, sensitive, specific, and the preferred testing method to identify most respiratory pathogens (Caliendo, 2011; Pammi, 2024; Yan et al., 2011). These tests may be a more reliable diagnostic test as they can be performed in just hours, do not require as large a volume of blood, and are not affected by antepartum antibiotics

(Pammi, 2024).

BioFire has updated their FDA approved respiratory panel tests, the FilmArray RP and RP2, to become the FilmArray RP2.1 panel test. The new test, RP2.1, has added SARS-CoV-2 as a target compared to the previous versions of the respiratory panels (BioFire, 2023d). The prior FilmArray RP2.1 is able to detect 18 viral (Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Severe Acute Respiratory Syndrome Coronavirus 2, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H3, Influenza A/H1-2009, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial Virus) and 4 bacterial (*Bordetella parapertussis, Bordetella pertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*) targets. This FilmArray RP2.1 panel test can detect the 22 targets in 45 minutes with a 97.1% sensitivity and 99.3% specificity (BioFire, 2023d).

GenMark Diagnostics has developed FDA-approved rapid ePlex® Respiratory Pathogen Panel (Uyeki et al.) and Respiratory Pathogen Panel 2 (RP2) tests. They can identify the most common bacterial and viral pathogens causing upper respiratory infections. The RP test can detect pathogens including Adenovirus, Coronavirus (229E, HKU1, NL63, OC43), Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A H1, Influenza A H1-2009, Influenza A H3, Influenza B, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Respiratory Syncytial Virus A, Respiratory Syncytial Virus B, *Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*. The RP2 test will detect the same pathogens along with SARS-CoV-2 (GenMark, 2023). The ePlex® Respiratory Pathogen Panel test was more efficient than a laboratory developed PCR assay resulting “in a significant decrease in time to result, enabling a reduction in isolation days in half of the patients,” and increasing the identification of the causative pathogen (van Rijn et al., 2018).

The BioCode Respiratory Pathogen Panel is the FDA approved low-cost test that can simultaneously detect respiratory pathogens in nasopharyngeal swabs. This test is designed in a 96-well microplate format. The following 17 pathogens can be identified with this panel: Adenovirus, Coronavirus (229E, OC43, HKU1, and NL63), Human Metapneumovirus A/B, Influenza A, including subtypes H1, H1 2009 Pandemic, and H3, Influenza B, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Respiratory Syncytial Virus A/B, Rhinovirus/Enterovirus, *Bordetella pertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* (BioCode, 2024b).

The NxTAG Respiratory Pathogen Panel, developed by Luminex, is able to simultaneously detect 20 pathogens (Influenza A, Influenza A H1, Influenza A H3, Influenza B, Respiratory Syncytial Virus A, Respiratory Syncytial Virus B, Rhinovirus/Enterovirus, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Human Metapneumovirus, Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Human Bocavirus, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*) in a single test. The CE Marked panel also detects *Legionella pneumophila* (Luminex, 2023a).

QIAGEN Science has developed the QIAstat-Dx Respiratory SARS-CoV-2 Panel, which is authorized by the FDA under an Emergency Use Authorization (EUA). It can detect the SARS-CoV-2 virus along with 20 other respiratory pathogens, including Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus A+B, Influenza A, Influenza A H1, Influenza A H3, Influenza A H1N1/pdm09, Influenza B, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Rhinovirus/Enterovirus, Respiratory Syncytial Virus

A+B, *Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae*. It is able to provide qualitative results within an hour and is for *in vitro* diagnostic use (QIAGEN, 2024). When compared with the currently WHO-recommended RT-PCR (WHO-RT-PCR), the QIAstat-Dx Respiratory Panel had a 97% agreement with the WHO-RT-PCR and a sensitivity of 100% and specificity of 93% (Visseaux et al., 2020).

Central Nervous System Panel

The brain is well protected from microbial invasion via the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB). Nonetheless, bacteria, fungi, viruses, and amoebae can infect the brain and the consequences are often fatal. Points of entry include the BBB, BCSFB, and the olfactory and trigeminal nerves (Dando et al., 2014). Meningitis, which is when the brain and/or spinal cord become inflamed, is typically caused by viral infections due to enteroviruses; other neurotropic viruses include herpes simplex viruses, human cytomegalovirus, varicella-zoster virus, and rabies virus (Dando et al., 2014). In the United States, bacterial meningitis is most commonly caused by *Streptococcus pneumoniae*, group B *Streptococcus, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes, and Escherichia coli* (CDC, 2024c). Fungal meningoencephalitis, which is described as inflammation of the brain and surrounding membranes, is often caused by *Cryptococcus, Histoplasma, Blastomyces, Coccidioides, and Candida* (CDC, 2024e). Meningococcal meningitis is typically caused by *Neisseria meningitidis* (CDC, 2024a). Other types of pathogens may enter the central nervous system. The increasing use of molecular tests for the detection of pathogens in cerebrospinal fluid (CSF) has redefined the diagnosis and management of central nervous system (CNS) infections such as meningitis and encephalitis. However, it is important that test results correlate to the probability of infection. According to Petti and Polage (2019), the number of false-positive test results increase when the multiplex PCR tests are ordered in the absence of an elevated leukocyte count or elevated protein level in the CSF. Hence, the predictive value of the test increases when the tests are ordered only for those patients with a moderate to high pretest probability of having CNS infections based on clinical presentation and CSF findings (Petti & Polage, 2024).

The evaluation of meningitis routinely includes molecular testing, particularly when the patient is suspected to have viral meningitis. Although use of Gram stain and culture is the gold standard for diagnosis of bacterial meningitis, multiplex PCR assays may be useful as an adjunct, especially in patients who have already received antibiotic treatment. Other lab findings (for example, CSF cell count, glucose, and protein analyses) should be used as a screening method prior to the performance of molecular testing. Molecular assays for meningitis caused by fungi, parasites, rickettsia, and spirochetes are in development at this time (Petti & Polage, 2024).

Similarly, molecular testing of CSF is recommended when viral encephalitis, especially encephalitis due to Herpesviridae, is suspected. For other viral encephalitis, the clinical sensitivity and predictive value of multiplex-PCR assays is unknown. Therefore, a negative result does not exclude infection, and a combined diagnostic approach, including other methods like serology, may be necessary to confirm the diagnosis. Multiplex PCR-based assays may be useful in certain cases of bacterial meningitis, especially when a slow-growing or uncultivable bacterium like *Coxiella burnetti* is involved. Molecular assays for encephalitis caused by fungi, parasites, rickettsia, and spirochetes need to be investigated further and are not routinely available at this time (Petti & Polage, 2024).

The FDA approved BioFire FilmArray meningitis/encephalitis panel can provide information on 14 different pathogens in one hour. This test uses 0.2 mL of cerebrospinal fluid, and is able to detect

bacteria (*Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*), viruses (Cytomegalovirus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Human parechovirus, and Varicella zoster virus) and yeast (*Cryptococcus neoformans/gattii*) (BioFire, 2023c). BioFire states that this panel has an overall sensitivity of 94.2% and a specificity of 99.8% (BioFire, 2023c).

Sepsis Panel

Sepsis, also known as blood poisoning, is the body's systemic immunological response to an infection. Sepsis occurs when an infection (in the lungs, skin, urinary tract or another area of the body) triggers a chain reaction in an individual (CDC, 2024b). Sepsis can lead to end-stage organ failure and death. Septic shock occurs when sepsis results in extremely low blood pressure and abnormalities in cellular metabolism. The annual incidence of severe sepsis and septic shock in the United States is 300 per 100,000 people; sepsis is "the most expensive healthcare problem in the United States" (Gyawali et al., 2019).

Sepsis-related mortality remains high, and inappropriate antimicrobial and anti-fungal treatment is a major factor contributing to increased mortality (Liesenfeld et al., 2014). Blood culture is the standard of care for detecting bloodstream infections, but the method has several limitations (Lamy et al., 2020). Fastidious, slow-growing, and uncultivable organisms are difficult to detect by blood culture, and the test sensitivity decreases greatly when antibiotics have been given prior to culture. Additionally, culture and susceptibility testing may require up to 72 hours to produce results. Multiplex PCR assays of positive blood culture bottles have a more rapid turnaround time and are not affected by the administration of antibiotics. Faster identification and resistance characterization of pathogens may lead to earlier administration of the appropriate antibiotic, resulting in better outcomes, and may lessen the emergence of antibiotic-resistant organisms (Banerjee et al., 2015).

The T2Bacteria Panel is the first "FDA-cleared test to identify sepsis-causing bacteria directly from whole blood without the wait for blood culture" (T2Biosystems, 2024). This panel is able to identify 50% of all bloodstream infections, 90% of all ESKAPE bacteria (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Escherichia coli*) pathogens, and 70% of all blood culture species identified in the emergency room with a 95% sensitivity and 98% sensitivity (T2Biosystems, 2024).

The Magicplex™ Sepsis Real-time Test by Seegene can identify more than 90 sepsis-causing pathogens with only 1 mL of whole blood. This test identifies both bacteria and fungi, as well as three drug resistance markers in only six hours (Seegene, 2020, 2023).

GenMark has developed three ePlex® Blood Culture Identification (BCID) Panels. These include the ePlex BCID-Gram Positive Panel (identifies 20-gram positive bacteria and four resistance genes), the ePlex BCID-Gran Negative Panel (identifies 21-gram negative bacteria and six resistance genes), and the ePlex BCID-Fungal Panel (identifies 15-fungal organisms) (GenMark, 2020).

BioFire has developed the FDA-cleared FilmArray Blood Culture Identification Panel (BCID). The original panel could identify 24 targets, but the newly expanded BCID2 panel can identify 43 targets. Targets include gram-positive bacteria (*Enterococcus faecalis, Enterococcus faecium, Listeria monocytogenes, Staphylococcus, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus lugdunensis, Streptococcus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes*), gram-negative bacteria (*Acinetobacter calcoaceticus-baumannii complex,*

Bacteroides fragilis, Enterobacterales, Enterobacter cloacae complex, Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae group, Proteus, Salmonella, Serratia marcescens, Haemophilus influenzae, Neisseria meningitidis, Pseudomonas aeruginosa, Stenotrophomonas maltophilia), yeast (*Candida albicans, Candida auris, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis, Cryptococcus neoformans/gattii)*, and antimicrobial resistance genes (BioFire, 2023a).

Urinary Tract Infection Panel

Urinary tract infections (UTIs) occur in the urinary system and can be either symptomatic or asymptomatic. UTIs can include cystitis, an infection of the bladder or lower urinary tract, pyelonephritis, an infection of the upper urinary tract or kidney, urosepsis, urethritis, and conditions such as bacterial prostatitis and epididymitis (Bonkat et al., 2023; Hooton & Gupta, 2024). Typically, in an infected person, bacteriuria and pyuria (the presence of pus in the urine) are present and can be present in both symptomatic and asymptomatic UTIs. A urine culture can be performed to determine the presence of bacteria and to characterize the bacterial infection (Meyrier, 2024).

Panels comprising common UTI pathogens are now commercially available. Firms such as MicroGenDX and NovaDX offer panels consisting of many different pathogens involved in UTIs (MicroGenDX, 2019a; NovaDX, 2023). The NovaDX is a qPCR based test which can detect 17 pathogens including bacteria (*Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus saprophyticus*, and *Streptococcus agalactiae*) and yeast (*Candida albicans*) (NovaDX, 2023).

Cardwell et al. (2016) evaluated the microbiology of UTIs in hospitalized adults. Approximately 308 patients were included, with a total of 216 identified pathogens. The authors separated patients into three groups; “community acquired (Group 1); recent healthcare exposure (Group 2); or a history of identification of an extended-spectrum beta lactamase (ESBL)-producing organism (Group 3).” *Escherichia coli* was found to be the most common pathogen, but the frequency differed between groups. Other commonly identified pathogens included *Pseudomonas aeruginosa* (Cardwell et al., 2016).

Medina and Castillo-Pino (2019) estimated the prevalence of certain pathogens in UTI (complicated or uncomplicated). The authors found that up to 75% of uncomplicated UTIs and up to 65% of complicated UTIs are caused by uropathogenic *Escherichia coli* (UPEC). Other commonly seen pathogens included *Enterococcus spp,* Group B Streptococcus, *K. pneumonia,* and *S. saprophyticus* (Medina & Castillo-Pino, 2019).

Wound Panel

Wounds (acute or chronic) are almost always colonized by microbes, thereby leading to a significant rate of infection. Panel testing many pathogens have been proposed as a method to quickly identify and therefore treat a wound infection (Armstrong & Meyr, 2024). These panels may be culture-based or nucleic acid-based; nucleic acid panels are typically touted for their speed compared to culture panels.

Firms, such as GenetWorx, Viracor, and MicroGenDX, offer comprehensive panels addressing many different common pathogens, resistance genes, and more. Genera, such as *Streptococcus,*

Enterococcus, and *Staphylococcus* are frequent targets of these panels. Different combinations of panels are available (GenetWorx, 2024; MicroGenDX, 2019b; Viracor, 2024).

The Wounds Pathogen Panel by GenetWorx can identify 30 targets including bacteria, fungi, and viruses. Targeted pathogens include *Enterococcus faecalis*, *Enterococcus faecium, Methicillin Resistant Staphylococcus aureus* (MRSA), *Methicillin Sensitive Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis, Streptococcus pyogenes* (Group A Strep), *Streptococcus agalactiae* (Group B Strep), *Streptococcus dysgalactiae* (Group C Strep), *Acinetobacter baumannii, Bacteroides fragilis, Bartonella henselea, Bartonella quintana, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Bartonella Quintana, Serratia marcescens, Candida albicans, Candida glabrata, Candida parapsilosis, Candida dubliniensis, Candida tropicalis, Candida krusei, Tricophyton metagrophytes, Trichophyton rubrum, Aspergillus fumigatus, Mycobacterium fortuitum*, Herpes Simplex Virus 1, Herpes Simplex Virus 2, and Herpes Simplex Virus 3 (GenetWorx, 2024).

The Viracor Skin and Soft Tissue Infection Panel can identify 19 bacterial targets using TEM-PCRTM (Target Enriched Multiplex Polymerase Chain Reaction). These bacterial targets include *Acinetobacter baumannii, Bacteroides spp., Citrobacter freundii, Clostridium novyi/septicum, Clostridium perfringens, Enterobacter aerogenes, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Kingella kingae*, Klebsiella spp., Morganella morganii, Proteus mirabilis, Proteus vulgaris, Staphylococcus aureus, MRSA- Meth. resistant S. aureus, Panton-Valentine leukocidin gene, Staphylococcus lugdunensis, Streptococcus pyogenes (Group A) and Pseudomonas aeruginosa. This test has not been approved by the FDA and has a two to three day turnaround time (Viracor, 2024).

Ray et al. (2013) described the incidence and microbiology of skin and soft tissue infections (SSTIs). The authors focused on members of a Northern California health plan, identifying 376262 patients with 471550 SSTIs. Approximately 23% of these infections were cultured, 54% of these cultures were pathogen-positive, and *Staphylococcus aureus* was found in 81% of these specimens. The researchers calculated the rate of diagnosed SSTIs to be 496 per 10000 person-years (Ray et al., 2013).

A comprehensive list of the main commercial pathogen panel tests mentioned above can also be found in the table below. This table was last updated on 03/27/2023.

Commercial Pathogen Panel Tests		
Type of Panel	**Name**	**Pathogens Identified**
Gastrointestinal	BioFire FilmArray Gastrointestinal Panel	22 targets including bacteria, parasites, and viruses
Gastrointestinal	Luminex xTAG Gastrointestinal Pathogen Panel	15 targets including bacteria, parasites, and viruses
Gastrointestinal	Biocode Gastrointestinal Pathogen Panel	17 targets including bacteria, parasites, and viruses
Respiratory	BioFire FilmArray Respiratory 2.1 (RP2.1) Panel	22 targets including viruses and bacteria

Respiratory	GenMark Diagnostics Rapid ePlex® Respiratory Pathogen Panel	17 targets including viruses and bacteria
Respiratory	GenMark Diagnostics Rapid ePlex® Respiratory Pathogen 2 Panel	18 targets including viruses and bacteria
Respiratory	BioCode Respiratory Pathogen Panel	17 targets including viruses and bacteria
Respiratory	Luminex NxTAG Respiratory Pathogen Panel	20 targets including viruses and bacteria
Respiratory	QIAGEN Sciences QIAstat-Dx Respiratory Pathogen Panel	20 targets including viruses and bacteria
Central Nervous System	BioFire FilmArray Meningitis/ Encephalitis Panel	14 targets including bacteria, viruses and yeast
Sepsis	T2Bacteria Panel	5 ESKAPE pathogens and potentially more targets
Sepsis	Magicplex™ Sepsis Real-time Test	90+ including bacteria and fungi
Sepsis	GenMark ePlex® Blood Culture Identification Panel (Gram-positive, Gram-negative and fungal)	56 bacteria and fungi
Sepsis	BioFire Blood Culture	43 targets including bacteria and yeast
Urinary Tract Infection	NovaDX UTI Test	17 targets including bacteria and yeast
Wound	GENETWORx PCR Wound Testing	30 targets including bacteria, fungi, mycobacteria, and viruses
Wound	Viracor Skin and Soft Tissue Infection Panel	19 bacterial targets

Clinical Utility and Validity

Several studies demonstrated the overall high sensitivity and specificity of the gastroenterology pathogen panels (Buss et al., 2015; Claas et al., 2013; Onori et al., 2014). Several studies have also indicated that gastrointestinal pathogen panels are more sensitive than culture, microscopy, or antigen detection, thus illustrating the potential of panels as a diagnostic tool for gastrointestinal infections (Buss et al., 2015; Couturier et al., 2011; Humphrey et al., 2016; Liu et al., 2014; Operario & Houpt, 2011). Zhang and colleagues concluded that using multiplex PCR assays in the work-up of infectious

gastroenteritis has the potential to improve the diagnosis (Zhang et al., 2015).

Numerous studies have examined the clinical utility of the BioFire FilmArray GI Panel. Stockmann et al. (2015) focused on comparing the accuracy in detecting etiologic agents, particularly *Clostridioides difficile*, in stool specimen of pediatric patients with diarrhea between the FilmArray GI Panel with various standard laboratory methods performed at the discretion of the physician. They found that "a potential aetiologic agent was identified in 46% of stool specimens by standard laboratory methods and in 65% of specimens tested using the FilmArray GI Panel (P<0.001)." This FilmArray GI Panel was also able to detect concurrent infections by diarrheal pathogens other than *C. difficile*, including norovirus in 12% of supposed *C. difficile*-only testing cases. The FilmArray GI Panel also detected a pathogen in 63% of cases without additional *C. difficile* testing performed, and even detected *C. difficile* in 8% of those cases. These results proved the FilmArray GI Panel to be critical in detecting other diarrheal pathogens, and co-infections with other infectious diarrheagenic agents (Stockmann et al., 2015).

Similar results for the FilmArray GI Panel were found in another study for acute diarrhea. In conducting a prospective study, Cybulski et al. (2018) found that FilmArray detected pathogens at a higher rate than culture and at a faster time (35.3% in 18 hours versus 6.0% in 47 hours). This rapidity and accuracy also allowed patients to receive targeted therapy and facilitated quicker discontinuation of empirical antimicrobial therapy, demonstrating an improved clinical sensitivity with the FilmArray GI Panel when compared to culture (Cybulski et al., 2018). Beal et al. (2018) investigated the impact of submitting patient stool specimen for testing by the FilmArray GI panel ("cases") and compared overall findings with control patients from the year prior. The researchers concluded that this panel contributed to reducing the number of days on antibiotics (1.73 days among cases versus 2.12 days among controls), reducing "average length of time from stool culture collection to discharge" (3.4 days among cases vs 3.9 days among controls), and reducing overall health care cost by $293.61. They also found results like the previous studies on the FilmArray GI panel, with increased comprehensiveness of detectable pathogens, and eliminating unnecessary testing and antibiotic use (Beal et al., 2018).

Axelrad et al. (2019) performed a retrospective comparative analysis of patients who underwent testing with the FilmArray GI panel from 2015-2017 and those who solely underwent conventional stool testing from 2012-2015. The FilmArray GI panel detected more pathogens (29.2% positive cases vs 4.1%) and reduced the need for additional endoscopic procedures and abdominal radiology imaging within 30 days following stool testing, as well as reduced chances of antibiotic prescription within 14 days following stool testing. The amassed literature communicates the great clinical utility and extended benefits from a multiplex PCR panel like the FilmArray GI Panel.

Zhan et al. (2020) performed a comparison of the BioFire FilmArray gastrointestinal panel and the Luminex xTAG Gastrointestinal Pathogen Panel for detecting diarrheal pathogens in China in a total of 243 diarrhea specimens. These two panels were highly consistent in detecting norovirus, rotavirus, and *Campylobacter*, but had low consistency in detecting *Cryptosporidium, Salmonella,* Shiga-toxin producing *Escherichia coli* (Banerjee et al.) and enterotoxigenic *Escherichia coli* (ETEC). The BioFire FilmArray panel was found to be more sensitive, but the Luminex xTAG Gastrointestinal Pathogen Panel was more specific. There appeared to be additional concern for how the Luminex xTAG Gastrointestinal Pathogen Panel yielded more false negatives when detecting ETEC as well (Zhan et al., 2020).

Jo et al. (2021) evaluated the use of the BioFire FilmArray gastrointestinal panel for pediatric patients

with diarrhea. The authors compared the FilmArray GI panel results to conventional PCR for *E. Coli* and Allplex GI-Bacteria Assay results. A total 184 stool samples were tested, and it was found that "The BioFire GI Panel demonstrated a sensitivity of 100% for 12 targets and a specificity of >95% for 16 targets." The authors conclude that the FilmArray GI panel is useful for rapid identification of enteropathogenesis in pediatric patients (Jo et al., 2021).

Truong et al. (2021) investigated pediatric healthcare management before and after BioFire FilmArray gastrointestinal panel results were received. The study included 172 children, 120 of which had positive results. Based on the FilmArray GI panel results, the healthcare management plan changed for 23% of patients, including changes to antibiotic treatments, hospitalizations, room isolations, prescription changes, and test cancelations. The authors conclude that the FilmArray GI panel results impacted healthcare management, especially related to antibiotic treatment (Truong et al., 2021). Yoo at al. (2021) also studied the healthcare management of children with acute diarrhea using the BioFire FilmArray gastrointestinal panel. A total of 182 patients were included in the study. "A significant reduction in antibiotic use was observed in the prospective cohort compared to historical cohort, 35.3% vs. 71.8%; $p < 0.001$), respectively." The authors conclude that, likely due to the high positive rate and rapid reporting, the FilmArray GI panel was clinically beneficial for children, especially in reducing antibiotic use and enabling early precaution and isolation (Yoo et al., 2021).

Nijhuis et al. (2017) compared the GenMark Diagnostics ePlex Respiratory Pathogen panel with laboratory-developed real-time PCR assays for detecting respiratory pathogens. The study included 343 clinical specimens. The RP panel found an agreement of 97.4% with the real-time PCR assay regarding 464 pathogens found. The RP panel detected 17 more pathogens than the real-time PCR, showing that this panel could improve the efficiency of diagnostic "sample-to-answer testing" and cost-effectiveness, despite potentially costing more (Nijhuis et al., 2017).

van Asten et al. (2021) evaluated the performance of the GenMark Diagnostics ePlex Respiratory Pathogen panel and the QIAGEN Sciences QIAstat-Dx Respiratory Pathogen panel. The authors specifically studied the detection of three bacterial targets: *Legionella pneumophila, Mycoplasma pneumoniae* and *Bordetella pertussis*. The study included 56 specimens taken from the lower respiratory tract, five of which were negative and the other 51 had previously tested positive on real-time PCR assays for the targets. "The QIAstat-Dx Respiratory Panel V2 (Uyeki et al.) assay detected all of the *L. pneumophila* and *B. pertussis* positive samples but only 11/15 (73.3 %) of the *M. pneumoniae* targets. The ePlex Respiratory Pathogen Panel (RPP) assay detected 10/14 (71.4 %) of the L. pneumophila targets, 8/12 (66.7 %) of the B. pertussis positive samples and 13/15 (86.7 %) of the M. pneumoniae targets." The authors concluded that the clinical performance of both panels depend on the bacterial lode and sample type (van Asten et al., 2021).

Mormeneo Bayo et al. (2022) compared real-time PCR with microscopy in detecting intestinal protozoa in children. The study used the Seegene Allplex Gastrointestinal panel for the real-time PCR. Five hundred stool samples were analyzed from children, 15 years of age and under, and grouped into two classifications based on if the children had or had not had clinical parasitosis. Based on microscopy, 6.2% of samples were positive. Based on real-time PCR, 51.2% of samples were positive. The authors concluded that "real-time PCR increases the detection of intestinal protozoa, being underdiagnosed by microscopy, especially D. fragilis, in which PCR is considered the most appropriate method for its detection" (Mormeneo Bayo et al., 2022).

Trujillo-Gómez et al. (2022) the diagnostic test accuracy of the FilmArray Meningitis/Encephalitis

panel. The authors perfmored a systematic review of 19 studies containing a total of 11,251 participants, and performed a random-effects bivariate meta-analysis of diagnostic test accuracy. Using CSF/blood samples, the sensitivity was estimated to be 89.5% and the specificity was estimated to be 97.4%. Using the "final diagnosis adjudication based on clinical/laboratory criteria" the sensitivity was estimated to be 92.1% and the specificity was estimated to be 99.2%. The authors note that the certainty of evidence was low. The authors conclude that the FilmArray Meningitis/Encephalitis panel "may have acceptable-to-high sensitivities and high specificities for identifying bacteria, especially for *S.pneumoniae*, and viruses, especially for HSV-2, and enteroviruses" but suboptimal sensitivities for *L.monocytogenes, H.influenzae, E.coli*, and HSV-1 (Trujillo-Gómez et al., 2022).

Yoo et al. (2019) compared the Seegene Allplex Gastrointestinal, Luminex xTAG Gastrointestinal Pathogen Panel, and BD MAX Enteric Assays to determine which was the most efficient in detecting gastrointestinal pathogens from clinical stool samples. A total of 858 stool samples were used in this study. "The overall positive percentage agreements of Seegene, Luminex, and BD MAX were 94% (258 of 275), 92% (254 of 275), and 78% (46 of 59), respectfully. For *Salmonella*, Luminex showed low negative percentage agreement because of frequent false positives (n = 31) showing low median fluorescent intensity. For viruses, positive/negative percentage agreements of Seegene and Luminex were 99%/96% and 93%/99%, respectively" (Yoo et al., 2019). Overall, the authors suggest that these assays are promising in the detection of gastrointestinal pathogens simultaneously. Mahony et al. (2009) concluded that multiplex PCR-based testing was the most cost-effective strategy for the diagnosis of respiratory virus infections in children and resulted in better patient outcomes (shorter hospital stays) at lower costs (Mahony et al., 2009). Ginocchio et al. (2009) compared the sensitivities, specificities, positive predictive values, and negative predictive values of four different Influenza A diagnostic tests, including rapid antigen, direct immunofluorescence, viral culture, and PCR panel. The authors inferred that the PCR panel test provided the best diagnostic option with the highest sensitivity for the detection of all influenza strains and identified a significant number of additional respiratory pathogens (Ginocchio et al., 2009). Subramony et al. (2016) reported the use of multiplex PCR-based assays for respiratory viruses in hospitalized patients resulted in decreased healthcare resource utilization, including decreased use of antibiotics and chest radiographs (Subramony et al., 2016). Babady et al. (2018) evaluated a new panel of 19 viruses and two bacteria (ePlex Respiratory Panel) with 2908 samples by comparing it to BioFire FilmArray. Overall agreement was >95% for all targets, and positive agreement ranged from 85.1% to 95.1%. Negative agreement ranged from 99.5% to 99.8% (Babady et al., 2018).

The Infectious Diseases Society of America (IDSA) stated that CSF RT-PCR can be one of the methods used for the diagnosis of rabies virus and enteroviral encephalitis (Tunkel et al., 2008). Several studies have evaluated the clinical impact of RT-PCR for the detection of enterovirus in the CSF of patients with aseptic meningitis (Ramers et al., 2000; Robinson et al., 2002; Stellrecht et al., 2002). These studies showed a reduction in unnecessary diagnostic and therapeutic intervention (for example, antibiotic use, ancillary tests, etc.), length of hospital stay, and hospital costs. Tzanakaki et al. (2005) evaluated a multiplex PCR assay for detection of *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type b, and concluded that the test had high sensitivity (between 88% and 93.9%), an overall specificity and positive predictive value of 100%, and a negative predictive value >99% (Tzanakaki et al., 2005). Leber et al. (2016) evaluated the performance of a commercially available multiplex PCR-based panel for meningitis and encephalitis, and concluded that the test is a sensitive and specific aid in diagnosis of CNS infections and leads to improved patient outcomes (Leber et al., 2016). Another study compared the FilmArray meningitis/encephalitis (ME)

panel by BioFire Diagnostics, which uses 0.2 mL of CSF to test for 14 pathogens in one hour (BioFire, 2023c), to traditional culture and PCR assay methods. The FilmArray ME panel "demonstrated an overall percent positive agreement (PPA) of 97.5% (78/80) for bacterial pathogens, 90.1% (145/161) for viruses, and 52% (26/50) for *Cryptococcus neoformans/C. gattii.* Despite the low overall agreement (52%) between the ME panel and antigen testing for detection of C. neoformans/C. gattii, the percent positive agreement of the FilmArray assay for *C. neoformans/C. gattii* was 92.3%" (Liesenfeld et al., 2014; Liesman et al., 2018). The ME panel has also been proven to aid in "decreasing the utilization of antibiotic therapy among pediatric patients admitted for concerns related to meningitis or encephalitis" (McDonald et al., 2020). Their research demonstrated that introducing the ME panel helped to reduce the days of therapy (DoT) from five days to three days and the number of inpatient days. Using the ME panel also decreased the empiric use of intravenous third generation cephalosporins and ampicillin for treatment independent of a respiratory viral pathogen diagnosis. Identifying the specific etiology guided more appropriate antibiotic therapy (McDonald et al., 2020).

The use of multiplex PCR assays to identify pathogens following positive blood culture can be faster than standard techniques involving phenotypic identification and antimicrobial susceptibility testing that is required up to 72 hours after the blood culture became positive (Liesenfeld et al., 2014). A prospective randomized controlled trial evaluating outcomes associated with multiplex PCR detection of bacteria, fungi, and resistance genes directly from positive blood culture bottles concluded that the testing led to more judicious antibiotic use (Banerjee et al., 2015). A study by Ward and colleagues compared the accuracy and speed of organism and resistance gene identification of two commercially available multiplex-PCR sepsis panels to conventional culture-based methods for 173 positive blood cultures. The researchers discovered that both the assays accurately identified organisms and significantly reduced the time to definitive results (on average, between 27.95 and 29.17 hours earlier than conventional method) (Ward et al., 2015). Another study assessed the diagnostic accuracy of a commercially available multiplex PCR-based assay for detecting infections among patients suspected of sepsis. They concluded that the test had high specificity with a modest sensitivity and had higher rule-in value than the rule-out value. If the patient had a positive result, a clinician can confidently diagnose sepsis and begin appropriate antimicrobial therapy while avoiding unwanted additional testing (Chang et al., 2013).

There are a few limitations with this type of testing. First, the level—detection or non-detection—of a microorganism does not necessarily imply a diagnosis. The tests can only describe the levels of microorganisms found in the environment, but additional information is required to make a diagnosis. Second, the scope of the 16S rRNA sequencing used in testing may be limited. Differences in regions more specific than rRNA (such as surface antigens or individual toxin genes) cannot be resolved with this test. For example, the test cannot distinguish between a pathogenic *C. difficile* strain and a nonpathogenic one. Moreover, the tests report some of their targets at a genus level only, which means that these targets cannot be differentiated at the species level (Almonacid et al., 2017; Watts et al., 2017). Finally, the PCR technique can introduce errors during the amplification leading to incorrect detection. PCR enzymes may accidentally create "artefacts" or otherwise incorrect sequences causing the detection or measurement of the microorganisms to be inaccurate (V. Wintzingerode et al., 1997).

Aichinger et al. (2008) studied the diagnostic gain of repeat testing for *C. difficile*. "351 individuals were tested only twice by PCR (12.4% of individuals tested by PCR). There were 92 individuals (3.2% of individuals tested by PCR) who had three or more PCR tests performed within seven days. In 85

(92.4%) cases, results of all tests were negative. There were no individuals who had positive results following an initial negative test. For six individuals (6.5%), the results switched from an initial positive to a subsequent negative result, while one patient (1.1%) demonstrated only positive results. They found that the use of repeat testing is unnecessary" (Aichinger, 2008).

UroSwab is a urine-based proprietary test from Medical Diagnostics LLC. UroSwab is a real-time PCR test intended to detect numerous pathogens potentially involved in sexually transmitted and urological infections. This test uses a patient's urine, and the turnaround time is estimated at 24-72 hours. The results include whether a pathogen's presence was normal or abnormal and includes comments on what the pathogen's presence means (Medical Diagnostics, 2024a, 2024b).

McCarty et al. (2023) tested the performance and clinical utility of the GenMark ePlex Blood Culture Identification Gram-Negative Panel. The authors used "matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry on bacterial isolates" as a reference to compare results. In total, 98.1% (106/108) of the bacteria identified by MALDI were on the GenMark panel, and "valid tests (107/108, 99.1%) yielded results on average 26.7 h earlier" (McCarty et al., 2023).

Guidelines and Recommendations

American College of Gastroenterology (ACG)

American College of Gastroenterology (ACG) stated that "diarrheal disease by definition has a broad range of potential pathogens particularly well suited for multiplex molecular testing. Several well-designed studies show that molecular testing now surpasses all other approaches for the routine diagnosis of diarrhea. Molecular diagnostic tests can provide a more comprehensive assessment of disease etiology by increasing the diagnostic yield compared with conventional diagnostic tests" (Riddle et al., 2016). Furthermore, the ACG recommended that "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)" (Riddle et al., 2016).

The ACG also notes:

- "Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks."
- "Stool diagnostic studies may be used if available in cases of dysentery, moderate–severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy" (Riddle et al., 2016).

In 2013, the ACG made the following recommendations on diagnostic tests used for Clostridium difficile infections (Surawicz et al., 2013):

- "Only stools from patients with diarrhea should be tested for Clostridium difficile. (Strong recommendation, high-quality evidence)"

- "Nucleic acid amplification tests (NAAT) for C. difficile toxin genes such as PCR are superior to toxins A + B EIA testing as a standard diagnostic test for CDI. (Strong recommendation, moderate-quality evidence)"
- "Glutamate dehydrogenase (GDH) screening tests for C difficile can be used in two- or three-step screening algorithms with subsequent toxin A and B EIA testing, but the sensitivity of such strategies is lower than NAATs. (Strong recommendation, moderate-quality evidence)"
- "Repeat testing should be discouraged. (Strong recommendation, moderate-quality evidence)"
- "Testing for cure should not be done. (Strong recommendation, moderate-quality evidence)" (Surawicz et al., 2013).

Infectious Diseases Society of America (IDSA)

In 2013, the IDSA stated that "molecular diagnostics that detect microbial DNA directly in blood have achieved a modest level of success, but several limitations still exist. Based on available data, well-designed multiplex PCRs appear to have value as sepsis diagnostics when used in conjunction with conventional culture and routine antibiotic susceptibility testing" (Caliendo et al., 2013).

The IDSA published guidelines for the diagnosis and management of infectious diarrhea which state:

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. However, other bacterial, viral, and parasitic agents should be considered regardless of symptoms. Any specimen testing positive for bacterial pathogens by culture independent diagnostics (such as an antigen based molecular assay) should be cultured in a clinical or public health laboratory if isolation was requested or required. Finally, clinical consideration should occur with interpretation of results of multi-pathogen NAATs as these tests only detect DNA and not necessarily pathogens (Shane et al., 2017).

The IDSA advises that repeat testing of gastrointestinal pathogen panels (GIP) utilizing multiplex NAATs is not considered medically necessary within seven days during the same period of diarrhea. (McDonald et al., 2018).

The IDSA acknowledges the availability of an FDA-approved multiplex PCR targeting 14 organisms for diagnosing encephalitis and meningitis, but the society states it "should not be considered a replacement for culture." The IDSA also notes that for gram-negative or gram-positive bacteria, bacterial culture is noted as the main diagnostic procedure (albeit at low sensitivity and optional). Regarding UTI, the IDSA only recommends nucleic acid testing for adenovirus and BK polyoma virus (Miller et al., 2018).

Regarding "wounds" (termed skin and soft tissue infections in the IDSA guideline), the IDSA typically recommends culture for most pathogens. Only a few strains of bacteria and viruses (such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus spp,* MRSA, and streptococci) were recommended for nucleic acid testing with the majority of bacterial and fungal pathogens recommended for culture instead (Miller et al., 2018).

The IDSA recommends RT-PCR or other molecular tests over other influenza tests in hospitalized patients. RT-PCR tests targeting a panel of respiratory pathogens are recommended in hospitalized,

immunocompromised patients (Uyeki et al., 2018).

The IDSA acknowledges that multiplex viral NAAT (potentially combined with bacferial NAAT) makes some clinical sense for immunocompromised and critically ill patients with pneumonia, as well as for those with exacerbations of airway disease. “These are situations where treatment of non–influenza viruses such as respiratory syncytial virus (RSV) or adenovirus may be considered (eg, in a stem-cell-transplant patient) and rapid test results are most likely to influence subsequent modifications of empiric broad-spectrum antibiotics” (Hanson et al., 2020). However, while the analytic sensitivity of multiplex NAAT decreases the likelihood that an important pathogen will be missed, enhanced detection can also complicate interpretation of results and available studies on the significance of mixed infections have reported variable results. IDSA notes that “additional studies are needed to understand whether coinfections portend poorer prognosis. . . High analytic sensitivity also translates to high negative-predictive values (ie, generally >97%, depending on prevalence), but there may be important differences among individual panel targets or across manufacturers. It is incumbent on clinicians and laboratorians to understand the test characteristics of each individual panel target, especially if the results inform antibiotic de-escalation in high-acuity settings. Even the largest multiplex panels do not detect all potential pathogens, and the optimal multiplex panel design remains a matter of debate. As a result, current tests are not yet a replacement for bacterial and fungal culture with antimicrobial susceptibility testing. Culture also remains essential for epidemiologic studies, vaccine-related decisions, and local antibiograms” (Hanson et al., 2020)

Global Wound Biofilm Expert Panel Consensus Guidelines

A Global Wound Biofilm Expert Panel have strongly agreed that “there are currently no routine diagnostic tests available to confirm biofilm presence” and that “the most important measure for future diagnostic tests to consider is indication of where the biofilm is located within the wound” (Schultz et al., 2017).

Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SCCM)

A collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine issued international guidelines for management of sepsis and septic shock. It states “in the near future, molecular diagnostic methods may offer the potential to diagnose infections more quickly and more accurately than current techniques. However, varying technologies have been described, clinical experience remains limited, and additional validation is needed before recommending these methods as an adjunct to or replacement for standard blood culture techniques” (Rhodes et al., 2017).

A 2020 update regarding “Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children” was published by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. In it, they acknowledge the presence of new molecular technologies, but remark that they are “currently relatively expensive, are not sufficient for all pathogens and antibiotic sensitivities, and are not universally available” (Weiss et al., 2020).

National Institute for Health and Care Excellence (NICE)

The NICE states there is “insufficient evidence to recommend the routine adoption in the NHS of the integrated multiplex polymerase chain reaction tests, xTAG Gastrointestinal Pathogen Panel, FilmArray GI Panel and Faecal Pathogens B assay, for identifying gastrointestinal pathogens in people

with suspected gastroenteritis." NICE acknowledges that the tests show promise but need further data on their clinical utility (NICE, 2017).

American Society for Microbiology/Association for Molecular Pathology/Association of Public Health Laboratories/College of American Pathologists/Infectious Diseases Society of America/Pan American Society for Clinical Virology

These societies made a joint statement regarding respiratory viral panels and noted three populations in which multiplex panels would be beneficial. Those populations were "immunocompromised hosts, adult patients appearing acutely ill who are potential hospital admissions, and critically-ill adult patients, particularly ICU patients" (American Society for Microbiology, 2017).

American College of Chest Physicians (CHEST)

The CHEST has recommended that outpatient adults with an acute cough and suspected pneumonia should not undergo routine microbiological testing because there is no need for such testing. However, testing may be considered if the results would change the therapeutic approach. Microbiological tests may include culture, serologic, and PCR testing (Hill et al., 2019).

Centers for Disease Control and Prevention

Regarding molecular tests that are commonly used for a *C. difficile* diagnosis, the CDC states that that "FDA-approved PCR assays are same-day tests that are highly sensitive and specific for the presence of a toxin-producing C. diff organism. . . Molecular assays can be positive for C. diff in asymptomatic individuals and those who do not have an infection. Patients with other causes of diarrhea might be positive, which leads to over-diagnosis and treatment. . . When using multi-pathogen (multiplex) molecular methods, read the results with caution as the pre-test probability of C. diff infection might be less" (CDC, 2024d).

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America

The IDSA and SHEA have stated that the best-performing method for detecting patients with a greater risk of a *C. difficile* infection from a stool sample is to "Use a stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory when there are no pre-agreed institutional criteria for patient stool submission (Figure 2) (weak recommendation, low quality of evidence)" (McDonald et al., 2018). These guidelines also state that repeat testing (within seven days) should not be performed. Panel testing is not specifically mentioned in these guidelines (McDonald et al., 2018).

The European Association of Urology

The EAU published urological infections guidelines. For uncomplicated UTIs (recurrent UTIs, cystitis, pyelonephritis), the EAU does not mention molecular testing at any point of the treatment algorithm; instead, they recommend bacterial culture or dipstick testing for diagnosis and recommending against extensive workup. The EAU notes that antimicrobial susceptibility testing should be performed in all cases of pyelonephritis, but their guidelines do not suggest any methods over another. In complicated

UTIs, the EAU recommends urine culture to identify cases of clinically significant bacteriuria (Bonkat et al., 2023).

American Society of Transplantation Infectious Diseases Community of Practice

These guidelines focus on identifying infections in transplant patients. Their recommendations are as follows:

"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* (La Hoz & Morris, 2019)

American Society for Clinical Pathology (ASCP, through ChoosingWisely)

The ASCP states "Do not routinely order broad respiratory pathogen panels unless the result will affect patient management." They further state that patient management may include "provid [ing] immediate diagnosis and potentially expedite management decisions" and list "rapid molecular or point of care tests for RSV, Influenza A/B, or Group A pharyngitis" as examples (ASCP, 2019).

Food and Drug Administration (FDA)

There are numerous FDA-approved pathogen panels. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

II. Applicable Codes

Code	Description	Comment
87154	Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets	

87483	Infectious agent detection by nucleic acid (DNA or RNA); central nervous system pathogen (eg, Neisseria meningitidis, Streptococcus pneumoniae, Listeria, Haemophilus influenzae, E. coli, Streptococcus agalactiae, enterovirus, human parechovirus, herpes simplex virus type 1 and 2, human herpesvirus 6, cytomegalovirus, varicella zoster virus, Cryptococcus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets	
87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, 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 (eg, 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 (eg, 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	
87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets	
87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets	
87633	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets	
87636	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) and influenza virus	

	types A and B, multiplex amplified probe technique	
87637	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) and influenza virus types A and B, and respiratory syncytial virus, multiplex amplified probe technique	
0068U	Candida species panel (C. albicans, C. glabrata, C. parapsilosis, C. kruseii, C tropicalis, and C. auris), amplified probe technique with qualitative report of the presence or absence of each species Proprietary test: MycoDART-PCR™ dual amplification real time PCR panel for 6 Candida species Lab/Manufacturer: RealTime Laboratories, Inc/MycoDART, Inc	
0086U	Infectious disease (bacterial and fungal), organism identification, blood culture, using rRNA FISH, 6 or more organism targets, reported as positive or negative with phenotypic minimum inhibitory concentration (MIC)-based antimicrobial susceptibility Proprietary test: Accelerate PhenoTest™ BC kit Lab/Manufacturer: Accelerate Diagnostics, Inc.	
0109U	Infectious disease (Aspergillus species), real-time PCR for detection of DNA from 4 species (A. fumigatus, A. terreus, A. niger, and A. flavus), blood, lavage fluid, or tissue, qualitative reporting of presence or absence of each species Proprietary test: MYCODART Dual Amplification Real Time PCR Panel for 4 Aspergillus species Lab/Manufacturer: RealTime Laboratories/MycoDART, Inc	
0112U	Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene Proprietary test: MicroGenDX qPCR & NGS For Infection Lab/Manufacturer: MicroGenDX	
0115U	Respiratory infectious agent detection by nucleic acid (DNA and RNA), 18 viral types and subtypes and 2 bacterial targets, amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected Proprietary test: ePlex Respiratory Pathogen (Uyeki et al.) Panel Lab/Manufacturer: GenMark Diagnostics, Inc	
0140U	Infectious disease (fungi), fungal pathogen identification, DNA (15 fungal targets), blood culture, amplified probe technique, each target reported as detected or not detected Proprietary test: ePlex® BCID Fungal Pathogens Panel	

	Lab/Manufacturer: GenMark Diagnostics, Inc	
0141U	Infectious disease (bacteria and fungi), gram-positive organism identification and drug resistance element detection, DNA (20 gram-positive bacterial targets, 4 resistance genes, 1 pan gram-negative bacterial target, 1 pan Candida target), blood culture, amplified probe technique, each target reported as detected or not detected Proprietary test: ePlex® BCID Gram-Positive Panel Lab/Manufacturer: GenMark Diagnostics, Inc	
0142U	Infectious disease (bacteria and fungi), gram-negative bacterial identification and drug resistance element detection, DNA (21 gram-negative bacterial targets, 6 resistance genes, 1 pan gram-positive bacterial target, 1 pan Candida target), amplified probe technique, each target reported as detected or not detected Proprietary test: ePlex® BCID Gram-Negative Panel Lab/Manufacturer: GenMark Diagnostics, Inc	
0152U	Infectious disease (bacteria, fungi, parasites, and DNA viruses), DNA, PCR and next-generation sequencing, plasma, detection of >1,000 potential microbial organisms for significant positive pathogens Proprietary test: Karius® Test Lab/Manufacturer: Karius Inc	
0240U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected Proprietary test: Xpert® Xpress CoV-2/Flu/RSV plus (SARS-CoV-2 and Flue targets) Lab/Manufacturer: Cepheid®	
0241U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper respiratory specimen, each pathogen reported as detected or not detected Proprietary test: Xpert® Xpress CoV-2/Flu/RSV plus (all targets) Lab/Manufacturer: Cepheid®	
0321U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 20 bacterial and fungal organisms and identification of 16 associated antibiotic-resistance genes, multiplex amplified probe technique Proprietary test: Bridge Urinary Tract Infection Detection and Resistance Test Lab/Manufacturer: Bridge Diagnostics	

0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi Proprietary test: Johns Hopkins Metagenomic Next-Generation Sequencing Assay for Infectious Disease Diagnostics Lab/Manufacturer: Johns Hopkins Medical Microbiology Laboratory	
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 Proprietary test: GI assay (Gastrointestinal Pathogen with ABR) Lab/Manufacturer: Lab Genomics LLC, Thermo Fisher Scientific	
0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab Proprietary test: Lesion Infection (Wound) Lab/Manufacturer: Lab Genomics LLC, Thermo Fisher Scientific	
0371U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogen, semiquantitative identification, DNA from 16 bacterial organisms and 1 fungal organism, multiplex amplified probe technique via quantitative polymerase chain reaction (qPCR), urine Proprietary test: Clear UTI Lab/Manufacturer: Lifescan Labs of Illinois, Thermo Fisher Scientific	
0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen Proprietary test: Respiratory Pathogen with ABR (RPX) Lab/Manufacturer: Lab Genomics LLC, Thermo Fisher Scientific	
0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine Proprietary test: Urogenital Pathogen with Rx Panel (UPX) Lab/Manufacturer: Lab Genomics LLC, Thermo Fisher	

	Scientific	
0441U	Infectious disease (bacterial, fungal, or viral infection), semiquantitative biomechanical assessment (via deformability cytometry), whole blood, with algorithmic analysis and result reported as an index Proprietary test: IntelliSep® test Lab/Manufacturer: Cytovale®	
0442U	Infectious disease (respiratory infection), myxovirus resistance protein a (mxa) and c-reactive protein (crp), fingerstick whole blood specimen, each biomarker reported as present or absent Proprietary test: FebriDx® Bacterial/NonBacterial Point-ofCare Assay Lab/Manufacturer: Lumos Diagnostics, LLC, Lumos Diagnostics, LLC	
0480U	Infectious disease (bacteria, viruses, fungi, and parasites), cerebrospinal fluid (CSF), metagenomic next-generation sequencing (DNA and RNA), bioinformatic analysis, with positive pathogen identification Proprietary test: Bacteria, Viruses, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid (MSCSF) Lab/Manufacturer: Mayo Clinic, Laboratory Developed Test	
0504U	Infectious disease (urinary tract infection), identification of 17 pathologic organisms, urine, realtime PCR, reported as positive or negative for each organism Proprietary test: Urinary Tract Infection Testing Lab/Manufacturer: NxGen MDx LLC	

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

III. Definitions

Term	Meaning

IV. Related Policies

Policy Number	Policy Description
AHS-M2057	Diagnosis of Vaginitis
AHS-M2097	Identification of Microorganisms using Nucleic Acid Probes
AHS-M2172	Onychomycosis Testing

Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Reference Materials

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VI. Revision History

Revision Date	Summary of Changes
09/04/2024	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: This policy is specific to pathogen panel testing in the outpatient setting. As such, the addition of a disclaimer was added to Section III and all CC were simplified to remove the repetitive statement “In the outpatient setting”. Section III now begins with: “This policy is specific to testing in the outpatient setting. Criteria below do not apply to testing allowances in situations other than the outpatient setting.” Now allowing up to 11 GIPs on a PCR-panel for all individuals; 11 GIPs no longer restricted to the immunocompromised. Results in a change to CC1 and removal of CC2. Added “no more often than once every 7 days” frequency restriction to CC1, edited CC for clarity and consistency following that addition. CC1 now reads: “1) For individuals with persistent diarrhea or diarrhea with signs or risk factors for severe disease (i.e., fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain), multiplex PCR-

	based panel testing (up to 11 gastrointestinal pathogens [GIPs]) no more often than once every 7 days MEETS COVERAGE CRITERIA." Addition of the disclaimer to the beginning of this section allows a clarity and consistency edit to simplify CC2, now reads: "2) For individuals who are displaying signs and symptoms of a respiratory tract infection (i.e., temperature ≥ 102°F, pronounced dyspnea, tachypnea, tachycardia), multiplex PCR-based panel testing (up to 5 respiratory pathogens) MEETS COVERAGE CRITERIA." Added CPT code 0480U, 0504U (effective date 10/1/2024)
03/06/2024	Off-cycle coding modification: Added CPT code 0441U, 0442U (effective date 04/01/2024). Removed CPT code 0416U (effective date 04/01/2024).

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