POLICY SECTIONS

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POLICY DESCRIPTON

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, 2015).

RELATED POLICIES

Policy Number	Policy Title
M2057	Diagnosis Of Vaginitis Including Multi-Target PCR Testing
M2097	Identification Of Microorganisms Using Nucleic Acid Probes
M2172	Onychomycosis Testing

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 Section VII of this policy document.

1) Multiplex PCR-based panel testing of gastrointestinal pathogens (GIP) up to **5** pathogens **MEETS COVERAGE CRITERIA** in any of the following situations* (See Note 1):

    a) Community-acquired diarrhea of ≥7 days duration; or

    b) Diarrhea with signs or risk factors for severe disease (fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain, hospitalization and/or immunocompromised state).

2) In the outpatient setting, multiplex PCR-based panel testing of gastrointestinal pathogens up to **11** pathogens **MEETS COVERAGE CRITERIA** <u>ONLY</u> in immunosuppressed or HIV positive patients AND any of the following situations* (See Note 1):

    a) Community-acquired diarrhea of ≥7 days duration; or

    b) Diarrhea with signs or risk factors for severe disease (fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain, hospitalization and/or immunocompromised state).

3) Multiplex PCR-based panel testing of up to **5** respiratory pathogens **MEETS COVERAGE CRITERIA** for patients displaying signs and symptoms of a respiratory tract infection, as evidenced by a

compatible clinical syndrome including at least one of the following: temperature of 102 or greater, pronounced dyspnea, tachypnea, or tachycardia.

4) In the outpatient setting, multiplex PCR-based panel testing of **12 or MORE** gastrointestinal pathogens **DOES NOT MEET COVERAGE CRITERIA.**

5) In the outpatient setting, multiplex PCR-based panel testing of **6 or MORE** respiratory pathogens **DOES NOT MEET COVERAGE CRITERIA**.

6) In the outpatient setting, multiplex PCR-based panel testing of pathogens in CSF **DOES NOT MEET COVERAGE CRITERIA.**

7) In the outpatient setting, molecular detection-based panel testing of bloodstream pathogens **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 a patient's illness.

8) Using molecular-based panel testing for general screening of microorganisms **DOES NOT MEET COVERAGE CRITERIA.** These tests include, but are not limited to the following:

    a) Molecular-based panel testing on stool samples, such as SmartGut™

    b) Molecular-based panel testing of vaginal swabs, such as SmartJane™

    c) Molecular-based panel testing on urine samples, such as UroSwab®

9) Molecular detection-based panel testing of urine pathogens for the diagnosis of urinary tract infections **DOES NOT MEET COVERAGE CRITERIA**.

10) In the outpatient setting, using molecular-based panel testing to screen for or diagnose wound infections (i.e. skin/soft tissue infections), including diagnostic testing to confirm biofilm presence, **DOES NOT MEET COVERAGE CRITERIA**.

Note 1: According to CMS LCD L37766, "A GIP test panel is a single service with a single unit of service (UOS =1). A panel cannot be unbundled and billed as individual components regardless of the fact that the GIP test reports multiple individual pathogens and/or targets. The panel is a closed system performed on a single platform, and as such, is a single test panel with multiple components (UOS=1). If *C. difficile* is not included in a GIP panel, testing for *C. difficile* may be reasonable and necessary when ordered in addition to a GIP bacterial pathogen panel and supported by documentation in the medical record (CMS, 2021)."

TABLE OF TERMINOLOGY

Term	Definition
ACG	American College of Gastroenterology
ASCP	American Society for Clinical Pathology
BBB	Blood-brain barrier

Term	Definition
BCID	Blood culture identification
BCSFB	Blood-cerebrospinal fluid barrier
CDC	Centers for Disease Control and Prevention
CDI	Clostridium difficile infections
CHEST	American College of Chest Physicians
CMS	Centers for Medicare and Medicaid
CNS	Central nervous system
CPT	Current Procedural Terminology
CSF	Cerebrospinal fluid
DNA	DNA
Dot	Days of therapy
EAU	European Association of Urology
ESICM	European Society of Intensive Care Medicine
ETEC	Enterotoxigenic *Escherichia coli*
EUA	Emergency use authorization
FDA	Food and Drug Administration
GDH	Glutamate dehydrogenase
GI	Gastrointestinal
GPP	Gastrointestinal pathogen panel
HIV	Human immunodeficiency virus
HPV	Human papillomavirus infection
IDSA	Infectious Diseases Society of America
LAMP	Loop-mediated isothermal amplification
Lcds	Local Coverage Determination
Ldts	Laboratory developed tests
ME	Meningitis/encephalitis
MRSA	*Methicillin Resistant Staphylococcus aureus*
MSSA	*Methicillin Sensitive Staphylococcus aureus*
NAATt	Nucleic acid amplification test
NICE	National Institute for Health and Care Excellence
NP	Nasopharyngeal
NPS	Nasopharyngeal swabs
PCR	Polymerase chain reaction
PLA	Proprietary laboratory analyses
PPA	Percent positive agreement
RNA	Ribonucleic acid
RP	Respiratory Pathogen
RP2	Respiratory Pathogen Panel 2
RPP	Respiratory Pathogen Panel

Term	Definition
RSV	Human respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
RV+	Respiratory Virus Plus Nucleic Acid Test
RVP	Respiratory Viral Panel
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCCM	Society of Critical Care Medicine
SHEA	Society for Healthcare Epidemiology of America
SOT	Solid organ transplant
SSTI	Skin and soft tissue infection
STEC	Shiga-toxin producing *Escherichia coli*
STX1	Shiga Toxin 1
STX2	Shiga Toxin 2
TEM-PCRTM	Target enriched multiplex polymerase chain reaction
UOS	Unit of service
UPEC	Uropathogenic *Escherichia coli*
UTI	Urinary tract infection
WGO	World Gastroenterology Organization
WHO	World Health Organization
WHO-RT-PCR	World Health Organization-recommended reverse transcriptase polymerase chain reaction

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 particular 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, 2015).

The Centers for Medicare and Medicaid Services (CMS, 2021) 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].”

Gastrointestinal Pathogen Panel

Approximately 2 billion cases of diarrheal disease occur worldwide every year, resulting in 1.9 million deaths in children younger than five years of age annually (Farthing et al., 2013). The Centers for Disease

Control and Prevention 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, Griffin, Angulo, Tauxe, & Hoekstra, 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, DuPont, & Connor, 2016). Further, healthcare and antibiotic associated diarrhea are mainly caused by toxin-producing *Clostridium difficile* causing more than 300,000 cases annually (CMS, 2021).

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, Morrison, & Tang, 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 new technique which uses PCR to detect Strongyloides in stool and urine samples (Fernandez-Soto et al., 2016), although it is not yet widely available (La Hoz & Morris, 2019).

Several proprietary panels for the assessment of gastrointestinal pathogens are available. BioFire Diagnostics offers an FDA-approved 22-target testing panel for the gastroenteritis, termed the BioFire FilmArray Gastrointestinal Panel. The panel's targets include bacteria (*Campylobacter, Clostridium difficile, Plesiomonas shigelloides*, *Salmonella, Yersinia enterocolitica, Vibrio (parahaemolyticus, vulnificus), Vibrio cholerae*, 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*), parasites (*Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica* and *Giardia lamblia*), and viruses (Adenovirus F40/41, Astrovirus, Norovirus GI/GII, Rotavirus A and Sapovirus (I, II, IV, and V)) (BioFire, 2019). 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, 2019).

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, 2020b)." 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* (STEC) stx1/stx2, *Salmonella, Shigella, Vibrio cholerae, Yersinia enterocolitica,* Adenovirus 40/41, Norovirus GI/GII, Rotavirus A, *Cryptosporidium*, *Entamoeba histolytica*, and *Giardia*.

The Biocode Gastrointestinal Pathogen Panel is also FDA approved and it 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), Salmonella, Shiga-like toxin producing *E. coli* stx1/stx2, Shigella/ Enteroinvasive *E. coli*, Vibro/ Vibro *parahemolyticus*, *Yersinia enterocolitica*, Adenovirus 40/41, Norovirus GI/GII, Rotavirus A, *Cryptosporidium*, *Entamoeba histolytica*, and *Giardia lamblia*) in stool samples (BioCode, 2020a). 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, 2020). Lower respiratory tract infections occur in the lungs and any airways below the larynx. Lower respiratory infections include pneumonia, bronchitis, tuberculosis and bronchiolitis (Hansen, Lykkegaard, Thomsen, & Hansen, 2020). The CDC (2019a) has stated that in travelers, viral pathogens are the most common cause of respiratory infections; “causative agents include rhinoviruses, respiratory syncytial virus, influenza virus, parainfluenza virus, human metapneumovirus, measles, mumps, adenovirus, and coronaviruses (CDC, 2019a).” Further, in travelers, bacterial pathogens are less common but include *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*.

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, i.e. 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, 2019; Yan, Zhang, & Tang, 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, 2019).

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, 2021). The prior FilmArray RP2 was able to detect 17 viral (Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, 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 now detect 22 targets in 45 minutes with a 97.1% sensitivity and 99.3% specificity (BioFire, 2021).

GenMark Diagnostics has developed FDA-approved rapid ePlex® Respiratory Pathogen Panel (RP) 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, 2020b). 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 14 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, 2020b).

The NxTAG Respiratory Pathogen Panel, developed by Luminex, is able to simultaneously detect 20 pathogens (Influenza A, Influenza A H1, Influenza A H3, 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 (Luminex, 2020a).

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 21 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, 2020). 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 do 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). Bacterial meningitis is most commonly caused by *Streptococcus pneumoniae*, followed by *Streptococcus agalactiae;* in children, *Neisseria meningitidis* is most likely to cause meningitis (Dando et al., 2014). Fungal meningoencephalitis, which is described as inflammation of the brain and surrounding membranes, is often caused by the yeast *Cryptococcus neoformans*; further, meningococcal meningitis is typically caused by *Neisseria meningitidis* (Dando et al., 2014). Many 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, 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, 2019).

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, 2019).

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, 2019).

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, 2020b). BioFire states that this panel has an overall sensitivity of 94.2% and a specificity of 99.8%.

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, 2019b). 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, Ramakrishna, & Dhamoon, 2019).

Sepsis-related mortality remains high, and inappropriate antimicrobial and anti-fungal treatment is a major factor contributing to increased mortality (Liesenfeld, Lehman, Hunfeld, & Kost, 2014). Blood culture is the standard of care for detecting bloodstream infections, but the method has several limitations. 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, 2019)." 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, 2019).

The Magicplex™ Sepsis Real-time Test by Seegene is able to 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).

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, 2020a).

BioFire has developed the FilmArray Blood Culture Identification Panel which can identify 24 gram - positive bacteria (*Enterococcus, Listeria monocytogenes, Staphylococcus, Staphylococcus aureus, Streptococcus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*), gram-negative bacteria (*Acinetobacter baumannii, Haemophilus influenzae, Neisseria meningitidis, Pseudomonas aeruginosa, Enterobacteriaceae, Enterobacter cloacae complex, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus,* and *Serratia marcescens*) and yeast (*Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis,* and *Candida tropicalis)* pathogens (BioFire, 2020a).

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 male-specific conditions, such as bacterial prostatitis and epididymitis (Bonkat et al., 2021; Hooton & Gupta, 2021). 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, 2019).

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, such as *Pseudomonas aeruginosa* (MicroGenDX, 2019a; NovaDX, 2019). 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, 2019).

Cardwell, Crandon, Nicolau, McClure, and Nailor (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 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, 2021). 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 *Staphlococcus,* are frequent targets of these panels, and many different combinations of panels are available (GenetWorx, 2019; MicroGenDX, 2019b; Viracor, 2019).

The Wounds Pathogen Panel by GenetWorx is able to identify 22 targets including bacteria, fungi, and viruses. Targeted pathogens include *Enterococcus faecalis*, *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), *Bacteroides fragilis, Bartonella henselea, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bartonella Quintana, Candida albicans, Candida glabrata, Candida parapsilosis, Candida dubliniensis, Candida tropicalis, Mycobacterium fortuitum*, Herpes Simplex Virus 1, Herpes Simplex Virus 2 and Herpes Simplex Virus 3 (GenetWorx, 2019).

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 (Viracor, 2019). This test has not been approved by the FDA and has a 2-3 day turnaround time.

Ray, Suaya, and Baxter (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 04/05/2021.

Commercial Pathogen Panel Tests		
Type of Panel	**Name**	**Pathogens Identified**
Gastrointestinal	BioFire FilmArray Gastrointestinal Panel	22 targets including bacteria, parasites and viruses

Commercial Pathogen Panel Tests		
Type of Panel	**Name**	**Pathogens Identified**
Gastrointestinal	Luminex xTAG Gastrointestinal Pathogen Panel	19 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	21 targets including viruses and bacteria
Respiratory	BioCode Respiratory Pathogen Panel	14 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	22 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)	Collectively identify 56 bacteria and fungi
Sepsis	BioFire Blood Culture	24 targets including bacteria and yeast
Urinary Tract Infection	NovaDX UTI Test	17 targets including bacteria and yeast
Wound	GenetWorx Wounds Pathogen Panel	22 targets including bacteria, fungi and viruses
Wound	Viracor Skin and Soft Tissue Infection Panel	19 bacterial targets

Clinical Validity and Utility

Several studies demonstrated the overall high sensitivity and specificity of the gastroenterology pathogen panels (Buss et al., 2015; Claas, Burnham, Mazzulli, Templeton, & Topin, 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, Lee, Zelyas, & Chui, 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, Tremblay, Toffel, Velez, and Rand (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* (STEC) and enterotoxigenic *Escherichia coli* (ETEC). The BioFire FilmArray panel was found to be more sensitive, but the Luminex xTAG Gastrointesinal Pathogen Panel was more specific. There appeared to be additional concern for how the Luminex xTAG Gastrointesinal Pathogen Panel yielded more false negatives when detecting ETEC as well (Zhan et al., 2020).

Nijhuis, Guerendiain, Claas, and Templeton (2017) compared the GenMark Diagnostics ePlex Respiratory Pathogen panel with laboratory-developed real-time PCR assays for detecting respiratory pathogens, and found that with 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.

Yoo et al. (2019) compared the Seegene Allplex Gastrointestinal, Luminex xTAG Gastrointestinal Pathogen Panel, and BD MAX Enteric Assays in an effort 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 conclude by suggesting that these assays are promising in the detection of gastrointestinal pathogens simultaneously.

Mahony and colleagues 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 and colleagues 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 and colleagues 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, Zachariah, Krones, Whittier, & Saiman, 2016). Babady et al. (2018) evaluated a new panel of 19 viruses and 2 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, Billman, Hartin, Ho, & Sawyer, 2000; Robinson et al., 2002; Stellrecht, Harding, Woron, Lepow, & Venezia, 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 and colleagues 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 and colleagues 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, 2020b), 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 *Cryptococcusneoformans/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 "decreas[ing] the utilization of antibiotic therapy among pediatric patients admitted for concerns related to meningitis or encephalitis" (D. McDonald, Gagliardo, Chiu, & Di Pentima, 2020). Their research demonstrated that introducing the ME panel helped to reduce the days of therapy (DoT) from 5 days to 3 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 (D. 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).

An example of multiplex PCR assays can be found with two of Ubiome's sequencing tests, SmartGut and SmartJane. Both tests use multiplex PCR to detect the presence of over 20 different microorganisms in biologically diverse environments. SmartGut measures a specimen's gut flora (such as *Dialister invisus* or *Lactococcus lactis*) whereas SmartJane measures a specimen's vaginal flora (such as *Lactobacillus iners* or *Treponema pallidum*). The tests propose that they can provide a health snapshot of the environment tested based on the levels of microorganisms detected. The procedures for each test are similar; both require the user to self-sample (a stool sample for SmartGut and a swab inside the vagina for SmartJane) and send the sample back to Ubiome where it is analyzed by their labs. The labs use Precision Sequencing technology to extract DNA from the microorganisms in the sample and Illumina Next-Generation to sequence the targeted genes. Then, phylogenetic algorithms are used to analyze and organize the DNA from those microorganisms. Finally, a clinical report detailing the levels of the targeted microorganisms is sent to the user and medical provider (Ubiome, 2018a). The report contains measurements of its targeted microorganisms, whether those measurements are within the normal reference ranges for certain conditions, and whether certain high danger pathogens are present (such as *C. difficile* for SmartGut or *Chlamydia trachomatis* for SmartJane). SmartJane also tests for 19 different HPV strains (Ubiome, 2018b, 2018c). Ubiome claims an average of 99% sensitivity and 100% specificity on the species-level targets for SmartGut and 97.4% sensitivity and 100% specificity for its genus-level targets, but no independent studies were found to support those claims (Ubiome, 2018a). However, these tests have since been discontinued.

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 such as SmartGut and SmartJane 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, Göbel, & Stackebrandt, 1997).

UroSwab is a urine-based proprietary test from Medical Diagnostics LLC. UroSwab is a real-time PCR test intended to detect numerous pathogens—53 different targets as of April 2019—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 (Diagnostics, 2015a, 2015b).

GUIDELINES AND RECOMMENDATIONS

American College of Gastroenterology (ACG) (Riddle et al., 2016; Surawicz et al., 2013)

American College of Gastroenterology 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).”

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)”

World Gastroenterology Organization (Farthing et al., 2013)
The World Gastroenterology Organization guidelines (Farthing et al., 2013) on acute diarrhea in adults and children have no recommendations for multiplex PCR testing.

Infectious Diseases Society of America (IDSA) (Caliendo et al., 2013; Miller et al., 2018; Shane et al., 2017; Uyeki et al., 2018)
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 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).

Global Wound Biofilm Expert Panel Consensus Guidelines (Schultz et al., 2017)
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 (Rhodes et al., 2017)
A joint 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, 2017)
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 (Microbiology, 2017)
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” (Microbiology, 2017).

The European Association of Urology (EAU) (Bonkat et al., 2021)

The EAU published an update to their guidelines on UTIs in 2021. 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., 2021).

American College of Chest Physicians (CHEST) (Hill et al., 2019)
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 (CDC, 2020)
Regarding molecular tests that are commonly used for a *C. difficile* diagnosis, the CDC states that "FDA-approved PCR assays, which test for the gene encoding toxin B, 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 individuals who are asymptomatic. When using multi-pathogen (multiplex) molecular methods, the results should be read with caution. In addition, patients with other causes of diarrhea might be positive, which could lead to over-diagnosis and treatment."

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) (L. C. McDonald et al., 2018)
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 preagreed institutional criteria for patient stool submission (Figure 2) (weak recommendation, low quality of evidence) (L. C. McDonald et al., 2018)." These guidelines also state that repeat testing (within 7 days) should not be performed. Panel testing is not specifically mentioned in these guidelines.

American Society of Transplantation Infectious Diseases Community of Practice (La Hoz & Morris, 2019)
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) (ASCP, 2019a, 2019b)
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, 2019a).

The ASCP recommends against testing "for community gastrointestinal stool pathogens in hospitalized patients who develop diarrhea after day 3 of hospitalization" and instead recommend considering testing for *C. difficile* (ASCP, 2019b).

APPLICABLE STATE AND FEDERAL REGULATIONS

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member (e.g., Local Coverage Determinations [LCDs]) or National Coverage Determinations [NCDs] for Medicare and/or state coverage for Medicaid), then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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. .

All of the below descriptions are taken from the FDA website.

Respiratory Pathogen Panels

On January 10, 2011 the FDA approved the Verigene® Respiratory Virus Plus Nucleic Acid Test (RV+) on the Verigene® System as a qualitative nucleic acid multiplex test intended to simultaneously detect and identify multiple respiratory virus nucleic acids in (NP) swab specimens from individuals with signs and symptoms of respiratory tract infection.

On February 17, 2012 the FDA approved the xTAG® Respiratory Viral Panel (RVP) as a qualitative nucleic acid multiplex test intended for the simultaneous detection and identification of multiple respiratory virus nucleic acids in nasopharyngeal swabs from individuals suspected of respiratory tract infections.

On September 10, 2012 the eSensor Respiratory Viral Panel (RVP) was approved as a qualitative nucleic acid multiplex in vitro diagnostic test intended for use on the eSensor XT-8 system for the simultaneous detection and identification of multiple respiratory viral nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals exhibiting signs and symptoms of respiratory infection.

On December 17, 2015 the FDA approved NxTAG® Respiratory Pathogen Panel as a qualitative test intended for use on the Luminex® MAGPIX® Instrument for the simultaneous detection and identification of nucleic acids from multiple respiratory viruses and bacteria extracted from nasopharyngeal swabs collected from individuals with clinical signs and symptoms of a respiratory tract infection.

On May 30, 2017 the FDA approved the FilmArray® Respiratory Panel 2 (RP2), a multiplexed nucleic acid test intended for use with FilmArray® 2.0 or FilmArray® Torch systems for the simultaneous qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals suspected of respiratory tract infections.

On June 9, 2017 the FDA approved the EPlex Respiratory Pathogen Panel as a multiplexed nucleic acid in vitro diagnostic test intended for use on the ePlex® Instrument for the simultaneous qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals exhibiting signs and symptoms of respiratory tract infection.

On August 30, 2017 the FDA approved the Idylla Respiratory (IFV-RSV) Panel, which is an in vitro assay intended for the qualitative detection of nucleic acids for Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype 2009 H1, H275Y mutation of Influenza A subtype 2009 H1, Influenza B and Respiratory Syncytial Virus (A and B) from nasopharyngeal swabs in viral transport media of adult and pediatric patients. The test uses the Idylla system to aid in the diagnosis of respiratory viral infection when used in conjunction with other clinical and laboratory findings.

On March 30, 2020, under emergency use authorization, the FDA approved the QIAstat-Dx Respiratory SARS-CoV-2 Panel as a multiplexed nucleic acid real-time PCR test intended for the qualitative detection and differentiation of nucleic acid from multiple respiratory viral and bacterial organisms, including the SARS-CoV-2 virus, in nasopharyngeal swabs (NPS) eluted in universal transport media collected from patients suspected of COVID-19 by their healthcare provider.

On October 8, 2020, under emergency use authorization, the FDA approved the EPlex Respiratory Pathogen Panel 2 as a multiplexed nucleic acid in vitro diagnostic test t intended for use on the ePlex Instrument for the simultaneous qualitative detection and differentiation of nucleic acids from multiple respiratory viral and bacterial organisms, including nucleic acid from Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), in nasopharyngeal swabs (NPS) eluted in viral transport media obtained from individuals suspected of respiratory viral infection consistent with COVID-19 by their healthcare provider.

On March 17, 2021, under emergency use authorization, approved the FilmArray® Respiratory Panel 2.1 (RP2.1), which is a multiplexed nucleic acid test intended for the simultaneous qualitative detection and differentiation of nucleic acids from multiple viral and bacterial respiratory organisms, including nucleic acid from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in nasopharyngeal swabs (NPS) obtained from individuals suspected of COVID-19 by their healthcare provider.

Blood Culture Pathogen Panels

On January 30, 2015 the FDA approved FilmArray Blood Culture Identification (BCID) Panel for use with the FilmArray 2.0.

On March 25, 2016 the FDA approved the Great Basin Staph ID/R Blood Culture Panel is a qualitative, multiplex, nucleic acid-based in vitro diagnostic assay intended for the simultaneous identification of nucleic acid from Staphylococcus aureus, Staphylococcus lugdunensis and various Staphylococcus species to the genus level and the detection of the mecA gene for methicillin resistance directly from patient positive blood culture specimens.

On June 22, 2017 the FDA approved FilmArray NGDS Warrior Panel.

Meningitis Pathogen Panels

On October 8, 2015 the FDA approved the FilmArray Meningitis/Encephalitis (ME) Panel as a qualitative multiplexed nucleic acid-based in vitro diagnostic test intended for use with FilmArray and FilmArray 2.0 systems. The FilmArray ME Panel is capable of simultaneous detection and identification of multiple bacterial, viral, and yeast nucleic acids directly from cerebrospinal fluid (CSF) specimens obtained via lumbar puncture from individuals with signs and/or symptoms of meningitis and/or encephalitis.

Gastrointestinal Pathogen Panels

On January 16, 2013 the FDA approved the Prodesse® ProGastro SSCS Assay as a multiplex real time PCR in vitro diagnostic test for the qualitative detection and differentiation of Salmonella, Shigella, and Campylobacter (C. jejuni and C. coli only, undifferentiated) nucleic acids and Shiga Toxin 1 (stx1) and Shiga Toxin 2 (stx2) genes. Shiga toxin producing E. coli (STEC) typically harbor one or both genes that encode for Shiga Toxins 1 and 2. Nucleic acids are isolated and purified from preserved stool specimens obtained from symptomatic patients exhibiting signs and symptoms of gastroenteritis.

On March 21, 2013 the FDA approved the xTAG® Gastrointestinal Pathogen Panel (GPP) as a multiplexed nucleic acid test intended for the simultaneous qualitative detection and identification of multiple viral, parasitic, and bacterial nucleic acids in human stool specimens from individuals with signs and symptoms of infectious colitis or gastroenteritis.

On May 2, 2014 the FDA approved the FilmArray Gastrointestinal (GI) Panel as a qualitative multiplexed nucleic acid-based in vitro diagnostic test intended for use with the FilmArray Instrument. The FilmArray GI Panel is capable of the simultaneous detection and identification of nucleic acids from multiple bacteria, viruses, and parasites directly from stool samples in Cary Blair transport media obtained from individuals with signs and/or symptoms of gastrointestinal infection.

On June 20, 2014 the FDA approved the Verigene Enteric Pathogens Nucleic Acid Test (EP) as a multiplexed, qualitative test for simultaneous detection and identification of common pathogenic enteric bacteria and genetic virulence markers from liquid or soft stool preserved in Cary-Blair media, collected from individuals with signs and symptoms of gastrointestinal infection.

On September 16, 2014 the FDA approved the e xTAG® Gastrointestinal Pathogen Panel (GPP) as a multiplexed nucleic acid test intended for the simultaneous qualitative detection and identification of multiple viral, bacterial and parasitic nucleic acids in human stool specimens or human stool in Cary Blair media from individuals with signs and symptoms of infectious colitis or gastroenteritis.

On May 2, 2017 the FDA approved the BD MAX Extended Enteric Bacterial Panel performed on the BD MAX System, as an automated in vitro diagnostic test for the direct qualitative detection and differentiation of enteric bacterial pathogens.

On July 12, 2017 the FDA approved the Great Basin Stool Bacterial Pathogens Panel is a multiplexed, qualitative test for the detection and identification of DNA targets of enteric bacterial pathogens. The Stool Bacterial Pathogens Panel is performed directly from Cary Blair or C&S Medium preserved stool specimens from symptomatic patients with suspected acute gastroenteritis, enteritis, or colitis and is performed on the Portrait™ Analyzer.

On November 29, 2018, the FDA approved the BD Max Enteric Viral Panel for use as an in vitro diagnostic test to detect and differentiate enteric viral pathogens, including Norovirus, Rotavirus, Adenovirus, Sapovirus, and human Astrovirus.

APPLICABLE CPT / HCPCS PROCEDURE CODES

CPT	Code Description
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

CPT	Code Description
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.
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 (RP) 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

CPT	Code Description
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 SARSCoV-2/Flu/RSV (SARS-CoV-2 & Flu targets only) 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 SARSCoV-2/Flu/RSV (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

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

Approval History

Type	Date	Action
Effective Date	7/1/2022	New Policy
Revision Date		

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APPENDIX

Reserved for State specific information. Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.