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Pathogen Panel Testing

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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.[1]

II. Related Policies

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

III. 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 (see Note 1), panel testing of up to **5** respiratory pathogens (antigen panel testing or multiplex PCR-based panel testing) **MEETS COVERAGE CRITERIA**.

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

4) Antigen panel testing or 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**.

NOTES:

Note 1: Signs and symptoms of a respiratory tract infection include fever, chills, fatigue, cough, rhinorrhea, anorexia, pharyngitis, vomiting, new ageusia or anosmia, headaches, myalgia, diarrhea, and weakness.[2] Additional signs and symptoms of a respiratory tract infection may be seen in individuals who are less than 18 years of age. These include irritability, decreased activity, nausea, rash, stomach pain, ear tugging/otalgia, vomiting after coughing, tachypnea, chest retractions/nasal flaring, grunting, wheezing, crackles, dehydration, cyanosis, apnea episodes, drooling, or refusal to eat. For infants, non-specific signs such as poor feeding, lethargy, and fussiness may present over clear localizing symptoms.[3-7]

IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
ASCP	American Society for Clinical Pathology
BBB	Blood-brain barrier
BCID	Blood culture identification panel
BCSFB	Blood-cerebrospinal fluid barrier
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CDI	Clostridioides difficile infections

CHEST	American College of Chest Physicians
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DOT	Days of therapy
EAEC	Enteroaggregative *Escherichia coli*
E. coli	*Escherichia coli*
EAU	European Association of Urology
EIEC	Enteroinvasive *Escherichia coli*
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
GIPs	Gastrointestinal pathogens
GPP	Gastrointestinal pathogen panel
HIV	Human immunodeficiency virus
HPV	Human papillomavirus infection
IDSA	Infectious Diseases Society of America
LAMP	Loop-mediated isothermal amplification
LCD	Local coverage determination
LDT	Laboratory developed test
ME	Meningitis/encephalitis
MRSA	*Methicillin resistant staphylococcus aureus*
MSSA	*Methicillin sensitive staphylococcus aureus*
NAAT	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
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

V. 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.[1]

The Centers for Medicare and Medicaid Services report that the top target pathogens causing foodborne 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]."[8]

Beyond molecular testing, antigen panel testing has become an increasingly utilized diagnostic approach. These panels can detect multiple pathogens simultaneously through antigen detection techniques, such as lateral flow immunoassays. While generally less sensitive than multiplex

PCR, antigen panels offer rapid results at a lower cost, making them effective for point-of-care testing, outbreak management, and initial screening.[9]

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.[10] 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.[11] 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).[12] Further, healthcare and antibiotic associated diarrhea are mainly caused by toxin-producing *Clostridioides difficile* causing more than 300,000 cases annually.[8]

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. For patients with severe gastrointestinal symptoms, the focus is on detecting the most common and clinically significant pathogens likely to cause serious illness, including bacterial, viral, and parasitic agents. Clinically a targeted panel of gastrointestinal pathogens (GIPs) effectively covers the primary pathogens associated with severe gastrointestinal infections, such as *Salmonella spp.*, *Shigella spp.*, *Campylobacter jejuni*, and *Escherichia coli* for bacterial causes; *Norovirus*, *Rotavirus*, and *Adenovirus* for viral causes; and *Giardia*, *Entamoeba histolytica*, and *Cryptosporidium* for parasitic infections.[12,13]

Infectious disease of the gastrointestinal (GI) tract represent a heterogenous group of conditions caused by a wide array of viral, bacterial, protozoal, and parasitic pathogens. Clinical presentation varies significantly, ranging from self-limited, non-inflammatory diarrhea to severe, persistent, or febrile dysenteric illness. Most acute, self-limited diarrheal illnesses – particularly those of short duration and non-inflammatory nature – do not require laboratory testing, as they are typically viral in origin and resolve without specific treatment or intervention.[14]

When it comes to gastrointestinal panels of 11+ targets, many of the studies available are not randomized controlled trials and rely on retrospective data or observational design, limiting their ability to establish causation. Additionally, the detection of certain pathogens, particularly viruses, does not necessarily correlate with active infection. This can lead to inappropriate treatment decisions, unnecessary antibiotic use and potential harm to patients. Major professional societies recommend limiting broad multiplex testing in outpatient settings.[14]

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.[15] 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.[16] 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.[16] 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,[17] although it is not yet widely available.[18]

Several proprietary panels are available for detecting gastrointestinal pathogens. The BioFire FilmArray Gastrointestinal Panel is an FDA-approved 22-target test that detects bacterial, viral, and parasitic pathogens, including *Campylobacter, Clostridioides difficile, Norovirus, Rotavirus A, and Giardia lamblia*. The manufacturer reports a sensitivity of 98.5% and specificity of 99.2%, with results available within one hour; however, the test has not been evaluated for immunocompromised patients.[19] The xTAG Gastrointestinal Pathogen Panel by Luminex is another FDA-approved multiplex test that identifies bacterial, viral, and parasitic nucleic acids in fresh and frozen stool samples. It is capable of detecting over 90% of gastroenteritis-causing agents, including *Salmonella, Shigella, Vibrio cholerae, Norovirus GI/GII, and Cryptosporidium,* with results available in as little as five hours.[20] Similarly, the Biocode Gastrointestinal Pathogen Panel is an FDA-approved test that utilizes a 96-well microplate to detect 17 diarrhea-causing pathogens, such as *Clostridioides difficile* toxins A/B, *Enterotoxigenic E. coli, Vibrio/Vibrio parahaemolyticus, Adenovirus 40/41, and Entamoeba histolytica*. This rapid multiplex assay is considered cost-effective and may aid in infection control.[21]

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. Pediatric patients may have different signs and symptoms of respiratory tract infections. Signs and symptoms of upper respiratory tract infections for children are: nasal congestion (rhinorrhea), fever, cough, irritability (poor feeding in infants), decreased activity, headache, nausea, rash (less common), stomach pain, ear tugging/otalgia, and vomiting after coughing.[3-6] For pharyngitis, CDC highlights sore throat, but notes that young children may not be able to verbalize this and present with drooling, refusal to eat, or irritability.[5] For lower respiratory tract infections, signs and symptoms for children can include: tachypnea, chest retractions/nasal flaring, grunting, wheezing, crackles, fever, dehydration, cyanosis (occasionally), and apnea episodes.[3,7] Infants and toddlers often present with non-specific signs (such as poor feeding, lethargy, and fussiness) rather than clear localizing symptoms. Regarding the common cold, the most common virus is rhinovirus; the bacteria that most commonly causes a sore throat (pharyngitis) is *Streptococcus pyogenes.*[22] Lower respiratory tract infections occur in the lungs and any airways below the larynx. Lower respiratory infections include pneumonia, bronchitis, tuberculosis and bronchiolitis.[23]

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.[24] 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.[25] 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.[26-28] 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.[26]

While multiplex nucleic acid amplification testing (NAAT) panels for respiratory pathogens offer rapid detection of a broad range of viral and bacterial targets—sometimes up to 33 pathogens—the clinical utility of these expanded panels remains limited in many patient populations. Although some studies have associated multiplex respiratory panel testing with decreased hospital length of stay, reduced admissions, and lower antibiotic use, these benefits appear to be driven largely by the detection of influenza alone. In most cases, results for non–influenza pathogens do not alter clinical decision-making, particularly in immunocompetent patients with mild or moderate illness.[9,29] Point-of-care influenza testing—whether antigen- or PCR-based—has shown a greater impact on clinical outcomes than broad multiplex testing.[30,31]

In addition, the interpretation of expanded panel results is complicated by several factors, including the detection of colonizing or non-pathogenic organisms, prolonged viral shedding, and co-infections of uncertain clinical relevance.[29,32] These findings may not change treatment plans, leading to low clinical actionability despite high analytic sensitivity.[29] Studies have also noted that multiplex panels can contribute to over-testing and high healthcare costs, with some assays priced in the hundreds to thousands of dollars. Smaller, targeted panels or limited NAATs focused on high-impact pathogens (e.g., influenza A/B, RSV, SARS-CoV-2) are increasingly favored for their balance of diagnostic efficiency, clinical relevance, and cost-effectiveness. Expanded multiplex testing may still have a role in specific populations, such as immunocompromised or critically ill patients, especially when limited panels yield negative results and clinical suspicion remains high.[29]

The BioFire FilmArray RP2.1 Panel is an FDA-approved test that detects 18 viral and 4 bacterial

respiratory pathogens, including Influenza A, Respiratory Syncytial Virus (RSV), Human Metapneumovirus, *Bordetella pertussis*, and *Mycoplasma pneumoniae*. The updated version includes SARS-CoV-2 and provides results in 45 minutes with a reported sensitivity of 97.1% and specificity of 99.3%.[33] The GenMark ePlex® Respiratory Pathogen Panel and RP2 Panel are FDA-approved tests that identify bacterial and viral pathogens responsible for upper respiratory infections. The RP test detects pathogens such as Adenovirus, Parainfluenza, RSV A/B, and *Chlamydia pneumoniae*, while the RP2 panel includes SARS-CoV-2.[34]

The BioCode Respiratory Pathogen Panel is an FDA-approved, low-cost test that uses a 96-well microplate format to detect 17 respiratory pathogens, including coronavirus (229E, OC43, HKU1, NL63), Influenza A/B, Rhinovirus/Enterovirus, and *Bordetella pertussis*.[35] NxTAG Respiratory Pathogen Panel v2, is an updated test that received FDA clearance in 2024 and includes SARS-CoV-2 among 19 viral and 2 bacterial targets.[36] The QIAGEN QIAstat-Dx Respiratory SARS-CoV-2 Panel, authorized under an FDA Emergency Use Authorization (EUA), identifies SARS-CoV-2 along with 20 other respiratory pathogens. It provides qualitative results within an hour and demonstrated a 97% agreement with WHO-recommended RT-PCR, with a sensitivity of 100% and specificity of 93%.[37,38]

Antigen-based respiratory panels provide a rapid method for detecting respiratory pathogens by identifying viral or bacterial proteins rather than genetic material. These tests are generally faster than PCR-based methods, delivering results in minutes to hours. While antigen tests may have lower sensitivity than molecular assays, they are highly specific and useful for point-of-care and outbreak settings.[9]

The FDA-approved BD Veritor™ Plus System, offers rapid antigen detection for influenza, RSV, and SARS-CoV-2 with results in under 30 minutes. This test is widely used in clinical and point-of-care settings due to its speed and ease of use, though its sensitivity may vary depending on viral load and timing of specimen collection.[39] At-home antigen tests offer a rapid, low-cost and convenient method for detecting respiratory pathogens in symptomatic individuals. These at-home test include the QuickFinder COVID-19/Flu Antigen Self-Test, developed by OSANG Healthcare, has received FDA 510(k) clearance and is designed to detect both COVID-19 and influenza antigens. It is intended for home use, delivers rapid results within 15 minutes and demonstrates a sensitivity of 90.6% for SARS-CoV-2, 89.7% for influenza A, and 86.0% for influenza B, with a specificity of 99.4% for SARS-CoV-2, 98.8% for influenza A, and 99.7% for influenza B.[40] Similarly, the Quidel Corporation's Quidel QuickVue® At-Home OTC COVID-19 Test is designed for the qualitative detection of SARS-CoV-2 antigens. This test provides results within 10 minutes and is authorized for non-prescription home use with self-collected nasal swab samples from individuals aged two years and older.[41]

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.[42] 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.[42] 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.*[43] Fungal meningoencephalitis, which is described as inflammation of the brain and surrounding membranes, is often caused by *Cryptococcus, Histoplasma, Blastomyces, Coccidioides, and Candida.*[44] Meningococcal meningitis is typically caused by *Neisseria meningitidis.*[45] 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 (2023), 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 pre-test probability of having CNS infections based on clinical presentation and CSF findings.[46]

The evaluation of meningitis routinely includes molecular testing, particularly when the patient is suspected of having 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.[46]

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.[46]

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*).[47] BioFire states that this panel has an overall sensitivity of 94.2% and a specificity of 99.8%.[47]

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.[48] 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."[49]

Sepsis-related mortality remains high, and inappropriate antimicrobial and anti-fungal treatment is a major factor contributing to increased mortality.[50] Blood culture is the standard of care for detecting bloodstream infections, but the method has several limitations.[51] 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.[52]

The T2Bacteria Panel is the first FDA-cleared test capable of identifying sepsis-causing bacteria directly from whole blood without requiring blood culture, detecting 50% of bloodstream infections and 90% of ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli*) with 95% sensitivity and 98% specificity.[53] Roche Diagnostics offer the Cobas ePlex® Blood Culture Identification (BCID) Panels. These FDA-cleared panels provide rapid pathogen identification directly from positive blood cultures. The system includes the BCID-GP Panel (detecting 20 gram-positive bacteria and four resistance genes), the BCID-GN Panel (identifying 21 gram-negative bacteria and six resistance genes), and the BCID-FP Panel (targeting 15 fungal organisms).[54] BioFire's FDA-cleared FilmArray BCID has expanded from detecting 24 targets to 43 in the BCID2 version, covering gram-positive bacteria (e.g., *Enterococcus faecalis, Staphylococcus aureus, Streptococcus pneumoniae*), gram-negative bacteria (e.g., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*), yeast (e.g., *Candida albicans, Candida auris, Cryptococcus neoformans*), and antimicrobial resistance genes.[55]

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.[56,57] 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.[58]

Several molecular diagnostic tests are available for detecting UTIs. MicroGenDX's UroKEY UTI panel utilizes next-generation sequencing (NGS) to identify a wide range of over 57,000 bacteria and fungi, offering comprehensive detection in as little as five days.[59] Pathnostics' Guidance® UTI test combines PCR and Pooled Antibiotic Susceptibility Testing (P-AST™) to identify 27 bacterial and yeast organisms as well as 32 antibiotic-resistance genes with a 95% sensitivity.[60]

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.[61] 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 wound pathogen panels that detect a variety of bacterial, fungal, and viral targets, as well as resistance genes. These panels frequently include common wound pathogens such as *Streptococcus, Enterococcus, and Staphylococcus*. The GenetWorx Wound Pathogen Panel identifies 30 targets, including *MRSA, MSSA, Streptococcus species, Pseudomonas aeruginosa, Candida species, and Herpes Simplex Virus*.[62] The Viracor Skin and Soft Tissue Infection Panel uses TEM-PCR™ to detect 19 bacterial targets, including *Acinetobacter baumannii, Enterococcus faecalis, Klebsiella spp., Proteus mirabilis, MRSA*, and *Pseudomonas aeruginosa*, though it is not FDA-approved and has a two to three-day turnaround time.[63] MicroGenDX also offers molecular-based wound infection panels utilizing qPCR and NGS for expanded pathogen identification and antimicrobial resistance profiling.[64]

A comprehensive list of the main commercial pathogen panel tests mentioned above can also be found in the table below.

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	Diasorin NxTAG Respiratory Pathogen Panel v2	21 targets including viruses and bacteria
Respiratory	QIAGEN Sciences QIAstat-Dx Respiratory Pathogen Panel	21 targets including viruses and bacteria

Respiratory (antigen)	BD Veritor™ Plus System	Influenza, RSV, and SARS-CoV-2 antigens
Respiratory (antigen)	OSANG QuickFinder COVID-19/Flu Antigen Self-Test	SARS-CoV-2 and influenza antigens
Respiratory (antigen)	Quidel QuickVue® At-Home OTC COVID-19	SARS-CoV-2 antigens
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	Roche Diagnostics Cobas ePlex® Blood Culture Identification Panel (gram-positive, gram-negative and fungal)	Ranges from 15-21 targets depending on the panel
Sepsis	BioFire FilmArray Blood Culture Identification Panel v2 (BCID2)	43 targets including bacteria and yeast
Urinary Tract Infection	MicroGenDX's UroKEY UTI panel	57,000targets including bacteria and yeast
Urinary Tract Infection	Pathnostics' Guidance® UTI test	27 organisms and 32 antibiotic-resistance genes
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 sensitivity and specificity of the gastroenterology pathogen panels.[65-67] Several studies have also indicated that gastrointestinal pathogen panels are more sensitive than culture, microscopy, or antigen detection.[65,68-71] Zhang, et al. (2015) concluded that using multiplex PCR assays in the workup of infectious gastroenteritis had the potential to improve the diagnosis.[16] However, Xie and colleagues, in a randomized controlled trial, found no differences between groups related to administration of patient care (intravenous fluid, antibiotic treatment, hospitalization, or diagnostic imaging) with use of the assay. The BioFire FilmArray test was not correlated with clinically significant reductions in the usage of health care resources or improved patient care outcomes.[72]

Cybulski, et al. (2018) found that the FilmArray GI Panel 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.[73] 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" slightly (3.4 days among cases vs 3.9 days among controls), and reducing overall health care cost by $293.61.[74]

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* and enterotoxigenic *Escherichia coli* (ETEC).[52] 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.[75]

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 assay detected all of the *L. pneumophila* and *B. pertussis* positive samples but only 11/15 (73.3%) of the *M. pneumoniae* targets.[77] 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.[76]

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."[78]

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.[50] 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.[52] A study by Ward, et al. (2015) 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).[79] 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 diagnose sepsis and begin appropriate antimicrobial therapy while avoiding unwanted additional testing.[80]

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 non-pathogenic 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.[81-83]

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.[84]

McCarty, et al. (2023) tested the performance and clinical utility of the GenMark ePlex BCID 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."[85]

VI. Guidelines and Recommendations

American College of Gastroenterology (ACG)

The 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."[12] 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)."[12]

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."[12]

In 2013, the ACG made the following recommendations on diagnostic tests used for *Clostridioides difficile (C. difficile)* infections:[86]

- "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)"
- "Repeat testing should be discouraged. (Strong recommendation, moderate-quality evidence)"
- "Testing for cure should not be done. (Strong recommendation, moderate-quality evidence)."[86]

In 2021, the ACG reaffirmed the above recommendations with a note that the bacterium was reclassified from *Clostridium difficile* to *Clostridioides difficile* based on updated genetic analysis in 2016.[87] AGP also updated their C. difficile guidelines to include the following recommendations:

- "Only individuals with symptoms suggestive of active CDI should be tested (3 or more unformed stools in 24 hours).
- CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (conditional recommendation, low quality of evidence)."[88]

The ACG states that "no single test is suitable to be used as a stand-alone test; use of a 2-step testing algorithm … is our preferred testing method for optimal diagnostic accuracy," recommending that a multistep approach is necessary because NAAT testing alone or GDH alone is not considered sufficient; it must be paired with either a toxin test or a multistep algorithm to ensure accurate diagnosis. "In this approach, stool is first tested using a highly sensitive NAAT or GDH test, and the second test is the more specific toxin EIA."[88]

Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)

The IDSA and the ASM have issued a comprehensive guideline for the utilizing the microbiology laboratory in the diagnosis of infectious diseases. While multiplex molecular panels improve diagnostic speed and accuracy, the IDSA caution that careful validation and clinical experience are needed for effective integration. Below are their panel testing recommendations organized by body system:

Gastrointestinal System

According to the 2024 IDSA Clinical Practice Guideline, laboratory testing to determine the cause of infectious gastroenteritis is considered medically necessary only in specific clinical

contexts. Testing is indicated for individuals presenting with moderate to severe diarrhea, including cases that are bloody, febrile, dysenteric, persistent in duration, or associated with a nosocomial setting. Testing is also appropriate for individuals who are immunocompromised, as they are at greater risk for complications and may require tailored clinical management. Outside of these scenarios, laboratory testing is not routinely recommended. Patients with non-inflammatory, self-limited diarrhea or acute gastroenteritis or short duration typically do not benefit from diagnostic testing, as the condition is most often viral and self-resolving.[14]

When testing is clinically appropriate, the use of culture independent diagnostic tests—such as multiplex molecular panels—is supported by IDSA for the detection of bacterial pathogens. However, for patients without risk factors or for those with likely viral etiology, such tests may not influence clinical decision-making and may result in unnecessary downstream interventions. Multiplex panels that include viral targets generally offer limited clinical utility in immunocompetent individuals, as viral gastroenteritis frequently resolves without specific treatment. The use of multiplex panels to detect parasitic pathogens may be considered medically appropriate in patients with diarrhea lasting more than seven days, particularly when initial workup is inconclusive and the patient is at risk for parasitic exposure. The guideline also notes that highly multiplexed assays can identify mixed infections and organisms of uncertain clinical significance, including enteroaggregative or enteropathogenic *Escherichia coli* and certain viral agents, where the role is pathogenesis and need for treatment remain unclear. In such cases, test results should be interpreted in the context of the patient's clinical presentation and risk profile.[14]

Stool cultures are designed to detect specific pathogens. "Routine stool culture in most laboratories is designed to detect *Salmonella spp.*, *Shigella spp.*, and *Campylobacter spp.*" More comprehensive syndromic panel tests are recommended for patients with diarrhea of unknown etiology, particularly those with relevant exposure risks. "Cryptosporidium and Giardia lamblia testing is often offered and performed together as the primary parasitology examination. Additional parasite examinations should follow if a travel history, risk factors or clinical symptoms suggest parasitic disease."[14]

Furthermore, NAATs and multiplex molecular panels are recommended for detecting bacterial, viral, and parasitic causes of gastroenteritis. These methods are more sensitive than culture and provide rapid results. For *Clostridioides difficile*, NAATs are recommended as part of a multistep algorithm to improve diagnostic accuracy and reduce the identification of colonized patients.[14]

The IDSA published guidelines for the diagnosis and management of infectious diarrhea in 2017 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.[89]

In 2018 the IDSA and the Society for Healthcare Epidemiology of America (SHEA) released a shared *Clostridioides difficile* guideline stating 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 (weak recommendation, low quality of evidence)." These guidelines also state that repeat testing (within seven days) should not be performed. Panel testing is not specifically mentioned in these guidelines.[90]

Respiratory System

The IDSA recommends that panel testing remain optional for outpatients or hospitalized patients with mild community-acquired pneumonia (CAP) with testing being more important for patients with severe illness or significant risk factors. The guidelines state "identification of a pathogen will focus the antibiotic management for a particular patient. In addition, identification of certain pathogens such as *Legionella* species, influenza viruses, and SARS-CoV-2 have important public health significance. Current IDSA/ATS practice guidelines consider diagnostic testing as optional for the patient who is not hospitalized or who is hospitalized with mild CAP."[14]

Blood culture panel testing is recommended that "in those patients who require admission for severe CAP or who have strong risk factors for MRSA or Pseudomonas aeruginosa, blood culture sets should be collected before initiating antimicrobial therapy."[14]

The IDSA advises using respiratory antigen tests for use in symptomatic patients for quick diagnosis, but caution that even negative results should be confirmed with NAAT in cases where COVID-19 is suspected. "Rapid antigen tests have been widely used in the diagnosis of COVID-19... In symptomatic patients, antigen tests have demonstrated a sensitivity of 70%–80%, but in the asymptomatic population, the sensitivity has ranged from 40% to 50%." For COVID-19, the IDSA highlights the use of panel tests that include SARS-CoV-2 as one of the targets. "Several FDA-cleared multiplex molecular panels include SARS-CoV-2 as one of the targets. These panels can detect a wide range of respiratory pathogens, including SARS-CoV-2, and provide rapid results."[14]

In terms of specific respiratory pathogens, the IDSA notes that "FDA-cleared NAAT platforms are available for detecting a broad range of respiratory viruses and some atypical bacteria (e.g., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*). These have largely replaced rapid antigen detection tests and culture in most institutions." Additionally, for hospitalized patients with severe CAP or strong epidemiological risk factors, the IDSA recommends pathogen panels for detecting respiratory pathogens, including viruses and atypical bacteria.[14]

Central Nervous System

The IDSA recommends "NAAT of CSF [cerebrospinal fluid] is more sensitive than viral culture for the diagnosis of enteroviral central nervous system infection... If the patient develops any signs of acute flaccid myelitis (AFM) or central nervous system involvement, testing of CSF is

recommended." They caution that specific NAATs may be necessary when multiplex tests do not cover all required targets. "Parechoviruses, which can cause disease similar to enteroviruses, require a specific NAAT for detection."[14]

Genitourinary System

The IDSA recommends that individuals at higher risk for sexually transmitted infections should get panel testing state that "Multiplex molecular assays for detection of several organisms associated with bacterial vaginosis are more specific and sensitive than syndromic assessment alone... Adding testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) identifies approximately 25% more infections in high-risk populations."[14]

Infectious Diseases Society of America (IDSA), the American Society for Microbiology (ASM), the Association for Molecular Pathology (AMP), and the Pan American Society for Clinical Virology

In a 2023 Joint Report by the Association for Molecular Pathology, American Society for Microbiology, Infectious Diseases Society of America, and Pan American Society for Clinical Virology, multiplex PCR panel tests are described as the "preferential use of molecular approaches for pathogen detection, with many clinical laboratories discontinuing conventional methods (e.g., viral culture) because of gains in performance and operational efficiency from the molecular assays."[29]

The report also notes that "the availability and simplicity of multiplex molecular panels have increased their adoption in a wide range of settings (e.g., community hospitals and large reference laboratories)."

However, this report emphasizes the "importance of diagnostic stewardship for the appropriate implementation of multiplex molecular panels by considering, for example, which patient population would benefit most from their use (eg, recommending use in hospitalized, immuncompromised hosts and limiting use for relatively healthy outpatient hosts)."[29]

The report also outlines limitations of syndromic multiplex panels, including their fixed target lists, vulnerability to decreased accuracy from evolving sequences, inability to differentiate between viable and nonviable organisms, and the potential to detect clinically irrelevant pathogens. As stated, "syndromic multiplex panels do not always displace standard-of-care practices and may add laboratory cost to patient care."[29]

Importantly the report recommends careful consideration by medical providers and laboratories before adopting a multiplex test stating that "At a minimum, before the laboratory invests time and resources to evaluate a new test, there should be some evidence of clinical validity and utility, a clinically relevant demand for the test, and, ideally, there should be a potential cost benefit for the hospital and/or laboratory… In addition to demonstrating analytical and clinical validity, laboratories are increasingly required to demonstrate the clinical utility (medical value) of a test in their patient population"[29]

Infectious Diseases Society of America (IDSA)

The IDSA advances infectious disease research, education, and clinical practice. The IDSA provides guidelines to support healthcare professionals in diagnosing, treating, and preventing infectious diseases. Below are recommendations from various current IDSA guidelines related to pathogen panel testing:

Respiratory System

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.[77]

In their 2020 Molecular Testing for Acute Respiratory Tract Infections guideline, the IDSA acknowledges that multiplex viral NAAT (potentially combined with bacterial 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."[91]

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 co-infections portend poorer prognosis. . . High analytic sensitivity also translates to high negative-predictive values (i.e., 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."[91]

The IDSA published guidelines on the diagnosis of COVID-19, recommending the use of multiplex molecular panel tests that include SARS-CoV-2 for rapid and accurate diagnosis in symptomatic individuals and those with known exposure. However, standard NAATs (like RT-PCR) are preferred over rapid antigen tests for higher accuracy. Panel testing should be carefully validated and used alongside clinical judgment.[92]

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."[93]

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."[94]

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."[95]

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."[96]

In 2023 the SCCM and The IDSA co-published a guideline update on evaluating new fevers in critically ill adult patients. They discussed the use of panel testing, particularly in respiratory infections, while acknowledging limitations in evidence for routine viral blood testing. Below are their recommendations:

- "For critically ill patients with new fever and suspected pneumonia, or new upper respiratory infection symptoms (e.g., cough), we suggest testing for viral pathogens using viral NAAT panels (weak recommendation, very low-quality evidence).
- The panel found insufficient evidence to issue a recommendation on performing routine blood testing for viral pathogens (e.g., herpesviruses, adenovirus) in immunocompetent patients in the ICU.
- For critically ill patients with a new fever, we recommend testing for SARS-CoV-2 by PCR based on levels of community transmission."[97]

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.[98]

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."[99]

For hospitalized patients with acute respiratory illness, the CDC recommends ordering "multiplex nucleic acid detection assay for influenza A/B/SARS-CoV-2.23 If not available, order SARS-CoV-2 nucleic acid detection assay or antigen detection assay and influenza nucleic acid detection assay."[100]

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.[56]

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.*[18]

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.[101]

VII. 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: http://www.cms.gov/medicare-

coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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 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.

VIII. 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
87428	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) and influenza virus types A and B
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
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

CPT	Code Description
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 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

CPT	Code Description
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
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
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
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-of Care 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, real-time PCR, reported as positive or negative for each organism Proprietary test: Urinary Tract Infection Testing Lab/Manufacturer: NxGen MDx LLC

CPT	Code Description
0531U	Infectious disease (acid-fast bacteria and invasive fungi), DNA (673 organisms), nextgeneration sequencing, plasma Proprietary test: NeXGenTM Fungal/AFB NGS Assay Lab/Manufacturer: Eurofins Viracor, LLC
0556U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific DNA and RNA by real-time PCR, 12 targets, nasopharyngeal or oropharyngeal swab, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected Proprietary test: HealthTrackRx Bronchitis, HealthTrackRx Lab/Manufacturer: Thermo Fisher Scientific
0563U	Infectious disease (bacterial and/or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 11 viral targets and 4 bacterial targets, qualitative RT-PCR, upper respiratory specimen, each pathogen reported as positive or negative Proprietary test: BIOFIRE® SPOTFIRE® Respiratory/Sore Throat (R/ST) Panel – Respiratory Menu Lab/Manufacturer: bioMérieux
0564U	Infectious disease (bacterial and/or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 10 viral targets and 4 bacterial targets, qualitative RT-PCR, upper respiratory specimen, each pathogen reported as positive or negative Proprietary test: BIOFIRE® SPOTFIRE® Respiratory/Sore Throat (R/ST) Panel – Sore Throat Menu, Lab/Manufacturer: bioMérieux

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

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X. Review/Revision History

Effective Date	Summary
10/15/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC2 and CC4 edited to add antigen panel testing, CC2 edited to move respiratory infection signs/symptoms into new Note 1. CC now read: 2) For individuals who are displaying signs and symptoms of a respiratory tract infection (see Note 1), panel testing of up to 5 respiratory pathogens (antigen panel testing or multiplex PCR-based panel testing) MEETS COVERAGE CRITERIA." "4) Antigen panel testing or multiplex PCR-based panel testing of 6 or more respiratory pathogens DOES NOT MEET COVERAGE CRITERIA." New Note 1: "Note 1: Signs and symptoms of a respiratory tract infection include fever, chills, fatigue, cough, rhinorrhea, anorexia, pharyngitis, vomiting, new ageusia or anosmia, headaches, myalgia, diarrhea, and weakness. Additional signs and symptoms of a respiratory tract infection may be seen in individuals who are less than 18 years of age. These include irritability, decreased activity, nausea, rash, stomach pain, ear tugging/otalgia, vomiting after coughing, tachypnea, chest retractions/nasal flaring, grunting, wheezing, crackles, dehydration, cyanosis, apnea episodes, drooling, or refusal to eat. For infants, non-specific signs such as poor feeding, lethargy, and fussiness may present over clear localizing symptoms."
07/01/2025	Added CPT code 87428; 0556U, 0563U, 0564U Removed CPT code 0240U, 0241U, 0369U, 0370U 0373U, 0374U
04/01/2025	Off-cycle coding modification: Added CPT code 0531U Client requested variance: Removed codes 87505, 87632, 87633, 87636, 87637, 0240U, 0241U
03/15/2025	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."
10/01/2024	Off-cycle coding modification: Added CPT code 0480U, 0504U
04/01/2024	Off-cycle coding modification: Added CPT code 0441U, 0442U Removed CPT code 0416U
10/01/2023	Off-cycle coding modification: Added CPT code 0416U
09/01/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: All CCs except CC7 edited for clarity and consistency. Reorganized CC8-10 so that specific infection panel tests are first (UTI, then wound), followed by the general screening. Removed PLA code 0330U. Added PLA codes 0369U, 0370U, 0371U, 0373U and 0374U.
01/01/2023	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria. Coverage criteria edited for clarity: C1 edited for clarity. Previously read "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):" Now reads: "Multiplex PCR-based panel testing of up to 5 gastrointestinal pathogens (GIP) MEETS COVERAGE CRITERIA in any of the following situations* (See Note 1):" CC2 edited for clarity. Previously read "In the outpatient setting, multiplex PCR-based panel testing of gastrointestinal pathogens up to 11 pathogens MEETS COVERAGE CRITERIA ONLY in immunosuppressed or HIV positive patients AND any of the following situations* (See Note 1):" Now reads "In the outpatient setting, multiplex PCR-based panel testing of up to 11 gastrointestinal pathogens MEETS COVERAGE CRITERIA ONLY in immunosuppressed or HIV positive patients who ALSO have any of the following situations* (See Note 1):" CC3 edited for clarity. Previously read: "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." Now reads: "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, including at least one of the following: a) A temperature ≥ 102°F b) Pronounced dyspnea, c) Tachypnea, or d) Tachycardia. CC7 edited for clarity- “bloodstream pathogens” to “pathogens in the blood”. Now reads: “In the outpatient setting, molecular detection-based panel testing of pathogens in the blood DOES NOT MEET COVERAGE CRITERIA.” Added CPT codes 0109U, 0323U, 0330U, 0321U
05/15/2022	Initial Policy Implementation