Pathogen Panel Testing AHS – G2149

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Description of Procedure or Service

Description
Infectious diseases can be caused by a wide range of pathogens. Conventional diagnostic methods like culture, microscopy with or without stains and immunofluorescence, and immunoassay often lack sensitivity and specificity and have long turnaround times. Panels for pathogens using multiplex amplified probe techniques and multiplex reverse transcription can detect and identify multiple pathogens in one test using a single sample (Palavecino, 2015).

Related Policies
Identification Of Microorganisms Using Nucleic Acid Probes AHS-M2097

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for pathogen panel testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pathogen Panel Testing is covered

1. Reimbursement for multiplex PCR-based panel testing of gastrointestinal pathogens is allowed in any of the following situations:
   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. Reimbursement for multiplex PCR-based panel testing of pathogens in CSF is allowed for patients with clinical features and laboratory findings consistent with a CNS infection.

3. Reimbursement for molecular detection-based panel testing of bloodstream pathogens is allowed for patients who have clinical findings consistent with sepsis and have a positive blood culture result.
4. Reimbursement for multiplex PCR-based panel testing of respiratory pathogens is allowed 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.

**When Pathogen Panel Testing is not covered**

1. Reimbursement is not allowed for the use of molecular-based panel testing for screening of microorganisms. 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 on vaginal swabs, such as SmartJane™
   
c. Molecular-based panel testing on urine samples, such as UroSwab®

2. Reimbursement is not allowed for the molecular detection-based panel testing of urine pathogens for the diagnosis of urinary tract infections.

3. In the outpatient setting, reimbursement is not allowed for 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.

**Policy Guidelines**

**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 infectious organism. They 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, 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).

**Gastrointestinal Pathogen Panel**

Approximately 2 billion cases of diarrheal disease occur worldwide every year, resulting in 1.9 million deaths in children younger than 5 years of age each year (Farthing et al., 2013). The Centers for Disease Control and Prevention has estimated that there are nearly 48 million cases of acute diarrheal infection occurring annually in the United States, at an estimated cost upwards of $150 million (Scallan, Griffin, Angulo, Tauxe, & Hoekstra, 2011). 31 major pathogens acquired in the United 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 episode 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).

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 suspected bacterial infection, but it is time-consuming and labor intensive. Stool culture also 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 being used in the diagnosis of infectious gastroenteritis. These assays have significantly improved workflow and diagnostic output in diagnosis of GI 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 are more comprehensive and detect bacterial, viral and parasitic pathogens.

Several proprietary panels for the assessment of GI pathogens are available. BioFire Diagnostics offers a 22-target testing panel for the gastroenteritis. Some of the panel’s targets include bacteria (such as Salmonella, Plesiomonas shigelloides, Vibrio cholerae), parasites such as Cryptosporidium, and viruses such as astrovirus. The manufacturer claims a sensitivity of 98.5% and specificity of 99.2% 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, 2019a).

**Respiratory Pathogen Panel**

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 had several limitations like being labor-intensive, slow turnaround time, and low sensitivity.

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, Chlamydia pneumoniae, and Legionella pneumophila. They are rapid, sensitive, specific, and the preferred tests for most of the respiratory pathogens (Caliendo, 2011; Weisman, 2017; Yan, Zhang, & Tang, 2011). These tests may be more reliable diagnostic tests as they can be performed in just hours, do not require as large a volume of blood, and are not affected by antepartum antibiotics (Weisman, 2019). BioFire has recently released a new respiratory tract panel test, RP2. Bordetella parapertussis was added as a target to the previous version of the respiratory panel (BioFire, 2019b).

**CNS Pathogen Panel**

The increasing use of molecular tests for the detection of pathogens in cerebrospinal fluid (CSF) has redefined the diagnosis and management of CNS infections such as meningitis and encephalitis. However, it is important that test results correlated 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, 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 to as a screening method prior to the performance of molecular testing. Molecular assays for meningitis caused by fungi, parasites, rickettsia and spirochetes need to be investigated further and are in development at this time (Petti, 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 bacteria 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 or recommended at this time (Petti, 2019).

**Sepsis Panel**

Sepsis related mortality remains high and inappropriate antimicrobial and anti-fungal treatment is a major factor contributing to the 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 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, result in better outcomes, and lessen the emergence of antibiotic-resistant organisms (Banerjee et al., 2015).

**UTI Panel**

Urinary tract infections (UTIs) can 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., 2018; Hooton & Gupta, 2018). 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, 2017). 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).

Cardwell et al evaluated the microbiology of UTIs in hospitalized adults. 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, Crandon, Nicolau, McClure, & Nailor, 2016).

Medina et al 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).
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**Wound Panel**

Wounds (acute or chronic) are almost always colonized by microbes, thereby leading to a significant rate of infection. Panels testing many pathogens have been proposed as a method to quickly identify and therefore treat a wound infection (Armstrong, 2019). These panels may be culture-based or nucleic acid-based; nucleic acid panels are typically touted for their speed compared to culture panels. Firms, such as GenetWorx, Viracor, and MicroGenDX, offer comprehensive panels addressing many different common pathogens, resistance genes, and more. Genera, such as *Streptococcus*, *Enterococcus*, and *Staphylococcus*, are frequent targets of these panels, and many different combinations of panels are available (GenetWorx, 2019; MicroGenDX, 2019b; Viracor, 2019).

Ray et al 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. 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, Suaya, & Baxter, 2013).

**Clinical Validity and Utility**

Several studies demonstrated the overall high sensitivity and specificity of the gastroenterology pathogen panel (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 and 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).

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 (Mahoney et al., 2009). Ginocchio and colleagues compared the sensitivities, specificities, positive predictive value and negative predictive value 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 multiple 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 evaluated the 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...
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93.9%), an overall specificity and positive predictive value of 100%, and a negative predictive value >99% (Tzanankaki 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 was a sensitive and specific aid in diagnosis of CNS infections and leads to improved patient outcomes (Leber et al. (2016).

The use of multiplex PCR assays to identify pathogens following positive blood culture can be faster than the standard techniques involving phenotypic identification and antimicrobial susceptibility testing that 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. They discovered that both the assays accurately identified organisms and significantly reduce the time to definitive results (on average, between 27.95 and 29.17 h earlier than conventional method) (Ward et al. (2015)). A 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).

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).
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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)
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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)

In 2013, Infectious Diseases Society of America (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 that:
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. Any specimens testing positive for bacterial pathogens by culture independent diagnostics (such as antigen based molecular assays) 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 states it “should not be considered a replacement for culture” (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).


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

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).

National Institute for Health and Care Excellence (NICE) (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).
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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., 2018)

The EAU published guidelines on UTIs in 2018. 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, but their guidelines do not suggest any methods over another. In complicated UTIs, the EAU recommends urine culture to identify particular strains of bacteria (Bonkat et al., 2018).

Applicable Federal Regulations

A search of the FDA database on 11/14/2019 using the term “pathogen panel” yielded 12 results, the term “respiratory panel” yielded 18 results, the term “blood culture panel” yielded 8 results, the term “meningitis panel” yielded 1 result, and the term “gastrointestinal panel” yielded 12 results. Five of these tests have been approved in 2019. Descriptions of some of these tests are shown below. Additional tests may be considered laboratory developed tests (LDTs); developed, validated and performed by individual laboratories. 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; 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 nasopharyngeal (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 FilmArray® Respiratory Panel 2 (RP2) is 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 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.

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 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 Blairor 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.

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

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.


BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Scientific Background and Reference Sources


Caliedo, A. M., Gilbert, D. N., Ginocchio, C. C., Hanson, K. E., May, L., Quinn, T. C., . . . the Infectious Diseases Society of, A. (2013). Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. *Clinical Infectious Diseases*, 57(suppl_3), S139-S170. doi:10.1093/cid/cit578


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Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for Multiplex PCR-based panel testing when it is considered to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019.

4/16/2019 Removed item B that concerns “travel-related diarrhea” from the When Covered section and added second paragraph stating that genetic panel sequencing testing methods such as SmartGut™ and SmartJane™, to identify microbes is investigational to the When Not Covered section. Updated policy guidelines and references. Medical Director review 4/2019. (jd)

10/1/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Related Policies added to Description section. Revised the indications under the When Not Covered section to include the nature of the sample as well as UroSwab®. The following codes were added to the Billing/Coding section: 0068U, 0086U, 0097U, 0098U, 0099U, 0100U, and code table removed. References updated. Medical Director review 8/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)

2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. Added items 2 and 3 to the When Not Covered section. Billing/Coding section: added the following codes 0107U, 0112U, 0140U, 0141U, 0142U, 0151U, 0152U. Medical Director review 12/2019. (jd)
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.