



MASSACHUSETTS

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Medical Policy

Pathogen Panel Testing

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Policy Number: 045

BCBSA Reference Number: N/A

Related Policies

Identification Of Microorganisms Using Nucleic Acid Probes [#555](#)

Policy¹

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of nucleic acid testing panel using amplified probe technique (with or without quantification of viral load) is considered **MEDICALLY NECESSARY** for the following microorganisms:

- Babesiosis
- Ehrlichiosis, unspecified
- Tick-borne rickettsiosis, unspecified
- Anaplasma phagocytophilum
- Babesia microti
- Borrelia miyamotoi
- Ehrlichia chaffeensis.

The use of the following nucleic acid testing panel (without quantification of viral load) may be considered **MEDICALLY NECESSARY** if all the criteria below is met:

- Respiratory Virus Panel
 - Panel has no more than 5 respiratory pathogens (targets) AND
 - Individual has signs/symptoms of a respiratory infection AND
 - Results will be used to guide or alter clinical management.

The use of respiratory virus panels with more than 5 targets is considered **INVESTIGATIONAL**, including, but not limited to:

- BioFire® Respiratory Panel 2.1
- QIAstat-Dx Respiratory SARS CoV-2 Panel
- ePlex® Respiratory Pathogen Panel 2

Note: Local Coverage Determination (L39027) Respiratory Pathogen Panel Testing should be followed for Medicare Advantage members. [See MP #132 Medicare Advantage Management](#)

The use of the following nucleic acid testing panel (with or without quantification of viral load for viral panel elements) including but not limited to, is considered **INVESTIGATIONAL**:

- Urinary tract infection panel
- Sepsis panel
- Bloodstream infection panel
- Wound panel (to screen for or diagnose wound infections (i.e., skin/soft tissue infections), including diagnostic testing to confirm biofilm presence)
- General Screening of Microorganisms. These tests include, but are not limited to the following:
 - Molecular-based panel testing on stool samples, such as SmartGut™
 - Molecular-based panel testing on vaginal swabs, such as SmartJane™
 - Molecular-based panel testing on urine samples, such as UroSwab®

Note: Gastrointestinal and central nervous system pathogen panels are addressed separately in medical policy #555 Identification of Microorganisms Using Nucleic Acid Probes.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is not required .
Commercial PPO and Indemnity	Prior authorization is not required .

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
87468	Infectious agent detection by nucleic acid (DNA or RNA); Anaplasma phagocytophilum, amplified probe technique
87469	Infectious agent detection by nucleic acid (DNA or RNA); Babesia microti, amplified probe technique
87478	Infectious agent detection by nucleic acid (DNA or RNA); Borrelia miyamotoi, amplified probe technique
87484	Infectious agent detection by nucleic acid (DNA or RNA); Ehrlichia chaffeensis, amplified probe technique

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO and Indemnity:

CPT Codes

CPT codes:	Code Description
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
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
87636	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) and influenza virus types A and B, multiplex amplified probe technique
87637	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]), influenza virus types A and B, and respiratory syncytial virus, multiplex amplified probe technique
0240U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected
0241U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper respiratory specimen, each pathogen reported as detected or not detected

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT code above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10-CM diagnosis codes:	Code Description
B33.0	Epidemic myalgia
B33.20	Viral carditis, unspecified
B33.21	Viral endocarditis
B33.22	Viral myocarditis
B33.23	Viral pericarditis
B33.24	Viral cardiomyopathy
B33.8	Other specified viral diseases
B34.0	Adenovirus infection, unspecified
B34.1	Enterovirus infection, unspecified
B34.2	Coronavirus infection, unspecified
B34.8	Other viral infections of unspecified site
B34.9	Viral infection, unspecified
B97.0	Adenovirus as the cause of diseases classified elsewhere
B97.21	SARS-associated coronavirus as the cause of diseases classified elsewhere
B97.29	Other coronavirus as the cause of diseases classified elsewhere
B97.4	Respiratory syncytial virus as the cause of diseases classified elsewhere
B97.81	Human metapneumovirus as the cause of diseases classified elsewhere

B97.89	Other viral agents as the cause of diseases classified elsewhere
J00	Acute nasopharyngitis [common cold]
J01.00	Acute maxillary sinusitis, unspecified
J01.01	Acute recurrent maxillary sinusitis
J01.10	Acute frontal sinusitis, unspecified
J01.11	Acute recurrent frontal sinusitis
J01.20	Acute ethmoidal sinusitis, unspecified
J01.21	Acute recurrent ethmoidal sinusitis
J01.30	Acute sphenoidal sinusitis, unspecified
J01.31	Acute recurrent sphenoidal sinusitis
J01.40	Acute pansinusitis, unspecified
J01.41	Acute recurrent pansinusitis
J01.80	Other acute sinusitis
J01.81	Other acute recurrent sinusitis
J01.90	Acute sinusitis, unspecified
J01.91	Acute recurrent sinusitis, unspecified
J02.0	Streptococcal pharyngitis
J02.8	Acute pharyngitis due to other specified organisms
J02.9	Acute pharyngitis, unspecified
J03.00	Acute streptococcal tonsillitis, unspecified
J03.01	Acute recurrent streptococcal tonsillitis
J03.80	Acute tonsillitis due to other specified organisms
J03.81	Acute recurrent tonsillitis due to other specified organisms
J03.90	Acute tonsillitis, unspecified
J03.91	Acute recurrent tonsillitis, unspecified
J04.0	Acute laryngitis
J04.10	Acute tracheitis without obstruction
J04.11	Acute tracheitis with obstruction
J04.2	Acute laryngotracheitis
J04.30	Supraglottitis, unspecified, without obstruction
J04.31	Supraglottitis, unspecified, with obstruction
J05.0	Acute obstructive laryngitis [croup]
J05.10	Acute epiglottitis without obstruction
J05.11	Acute epiglottitis with obstruction
J06.0	Acute laryngopharyngitis
J06.9	Acute upper respiratory infection, unspecified
J09.X1	Influenza due to identified novel influenza A virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J10.00	Influenza due to other identified influenza virus with unspecified type of pneumonia
J10.01	Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J10.2	Influenza due to other identified influenza virus with gastrointestinal manifestations
J10.81	Influenza due to other identified influenza virus with encephalopathy
J10.82	Influenza due to other identified influenza virus with myocarditis
J10.83	Influenza due to other identified influenza virus with otitis media
J10.89	Influenza due to other identified influenza virus with other manifestations
J11.00	Influenza due to unidentified influenza virus with unspecified type of pneumonia

J11.08	Influenza due to unidentified influenza virus with specified pneumonia
J11.1	Influenza due to unidentified influenza virus with other respiratory manifestations
J11.2	Influenza due to unidentified influenza virus with gastrointestinal manifestations
J11.81	Influenza due to unidentified influenza virus with encephalopathy
J11.82	Influenza due to unidentified influenza virus with myocarditis
J11.83	Influenza due to unidentified influenza virus with otitis media
J11.89	Influenza due to unidentified influenza virus with other manifestations
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.3	Human metapneumovirus pneumonia
J12.81	Pneumonia due to SARS-associated coronavirus
J12.82	Pneumonia due to coronavirus disease 2019
J12.89	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J16.8	Pneumonia due to other specified infectious organisms
J18.0	Bronchopneumonia, unspecified organism
J18.1	Lobar pneumonia, unspecified organism
J18.2	Hypostatic pneumonia, unspecified organism
J18.8	Other pneumonia, unspecified organism
J18.9	Pneumonia, unspecified organism
J20.0	Acute bronchitis due to Mycoplasma pneumoniae
J20.1	Acute bronchitis due to Hemophilus influenzae
J20.2	Acute bronchitis due to streptococcus
J20.3	Acute bronchitis due to coxsackievirus
J20.4	Acute bronchitis due to parainfluenza virus
J20.5	Acute bronchitis due to respiratory syncytial virus
J20.6	Acute bronchitis due to rhinovirus
J20.7	Acute bronchitis due to echovirus
J20.8	Acute bronchitis due to other specified organisms
J20.9	Acute bronchitis, unspecified
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms
J21.9	Acute bronchiolitis, unspecified
J22	Unspecified acute lower respiratory infection
J40	Bronchitis, not specified as acute or chronic
J98.8	Other specified respiratory disorders
J98.9	Respiratory disorder, unspecified
R00.0	Tachycardia, unspecified
R04.0	Epistaxis
R04.1	Hemorrhage from throat
R04.2	Hemoptysis
R04.81	Acute idiopathic pulmonary hemorrhage in infants
R04.89	Hemorrhage from other sites in respiratory passages
R04.9	Hemorrhage from respiratory passages, unspecified
R05.1	Acute cough
R05.2	Subacute cough
R05.3	Chronic cough
R05.4	Cough syncope
R05.8	Other specified cough

R05.9	Cough, unspecified
R06.00	Dyspnea, unspecified
R06.01	Orthopnea
R06.02	Shortness of breath
R06.03	Acute respiratory distress
R06.09	Other forms of dyspnea
R06.1	Stridor
R06.2	Wheezing
R06.3	Periodic breathing
R06.4	Hyperventilation
R06.5	Mouth breathing
R06.6	Hiccough
R06.7	Sneezing
R06.81	Apnea, not elsewhere classified
R06.82	Tachypnea, not elsewhere classified
R06.83	Snoring
R06.89	Other abnormalities of breathing
R06.9	Unspecified abnormalities of breathing
R07.0	Pain in throat
R07.1	Chest pain on breathing
R07.2	Precordial pain
R07.81	Pleurodynia
R07.82	Intercostal pain
R07.89	Other chest pain
R07.9	Chest pain, unspecified
R09.01	Asphyxia
R09.02	Hypoxemia
R09.1	Pleurisy
R09.2	Respiratory arrest
R09.3	Abnormal sputum
R09.81	Nasal congestion
R09.82	Postnasal drip
R09.89	Other specified symptoms and signs involving the circulatory and respiratory systems
R10.0	Acute abdomen
R10.10	Upper abdominal pain, unspecified
R10.11	Right upper quadrant pain
R10.12	Left upper quadrant pain
R10.13	Epigastric pain
R10.2	Pelvic and perineal pain
R10.30	Lower abdominal pain, unspecified
R10.31	Right lower quadrant pain
R10.32	Left lower quadrant pain
R10.33	Periumbilical pain
R10.83	Colic
R10.84	Generalized abdominal pain
R10.9	Unspecified abdominal pain
R11.0	Nausea
R11.10	Vomiting, unspecified
R11.11	Vomiting without nausea
R11.12	Projectile vomiting
R11.2	Nausea with vomiting, unspecified

R13.10	Dysphagia, unspecified
R13.11	Dysphagia, oral phase
R13.12	Dysphagia, oropharyngeal phase
R13.13	Dysphagia, pharyngeal phase
R13.14	Dysphagia, pharyngoesophageal phase
R14.1	Gas pain
R14.2	Eructation
R14.3	Flatulence
R15.0	Incomplete defecation
R15.1	Fecal smearing
R15.2	Fecal urgency
R16.0	Hepatomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified
R19.4	Change in bowel habit
R19.5	Other fecal abnormalities
R19.7	Diarrhea, unspecified
R19.8	Other specified symptoms and signs involving the digestive system and abdomen
R21	Rash and other nonspecific skin eruption
R50.81	Fever presenting with conditions classified elsewhere
R50.9	Fever, unspecified
R51.0	Headache with orthostatic component, not elsewhere classified
R51.9	Headache, unspecified
R53.1	Weakness
R53.81	Other malaise
R53.83	Other fatigue
R55	Syncope and collapse
R56.00	Simple febrile convulsions
R56.01	Complex febrile convulsions
R56.9	Unspecified convulsions
R57.0	Cardiogenic shock
R57.1	Hypovolemic shock
R57.8	Other shock
R57.9	Shock, unspecified
R59.0	Localized enlarged lymph nodes
R59.1	Generalized enlarged lymph nodes
R59.9	Enlarged lymph nodes, unspecified
R60.0	Localized edema
R60.1	Generalized edema
R60.9	Edema, unspecified
R63.30	Feeding difficulties, unspecified
R63.31	Pediatric feeding disorder, acute
R63.32	Pediatric feeding disorder, chronic
R63.39	Other feeding difficulties
R65.10	Systemic inflammatory response syndrome (SIRS) of non-infectious origin without acute organ dysfunction
R65.11	Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction
R65.20	Severe sepsis without septic shock
R65.21	Severe sepsis with septic shock
R68.0	Hypothermia, not associated with low environmental temperature

R68.11	Excessive crying of infant (baby)
R68.12	Fussy infant (baby)
R68.13	Apparent life threatening event in infant (ALTE)
R68.19	Other nonspecific symptoms peculiar to infancy
R68.2	Dry mouth, unspecified
R68.83	Chills (without fever)
R68.84	Jaw pain
R68.89	Other general symptoms and signs
R69	Illness, unspecified
R91.1	Solitary pulmonary nodule
R91.8	Other nonspecific abnormal finding of lung field
R94.138	Abnormal results of other function studies of peripheral nervous system
R94.2	Abnormal results of pulmonary function studies
R94.30	Abnormal result of cardiovascular function study, unspecified
R94.31	Abnormal electrocardiogram [ECG] [EKG]
R94.39	Abnormal result of other cardiovascular function study
R94.8	Abnormal results of function studies of other organs and systems
R79.81	Abnormal blood-gas level
U07.1	COVID 19

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:**

CPT Codes

CPT codes:	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
87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets
87633	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets
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
0112U	Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene
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
0140U	Infectious disease (fungi), fungal pathogen identification, DNA (15 fungal targets), blood culture, amplified probe technique, each target reported as detected or not detected

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
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
0152U	Infectious disease (bacteria, fungi, parasites, and DNA viruses), microbial cell-free DNA, plasma, untargeted next-generation sequencing, report for significant positive pathogens
0202U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
0223U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
0225U	Infectious disease (bacterial or viral respiratory tract infection) pathogen-specific DNA and RNA, 21 targets, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected
0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab
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
0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score
0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine

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).

There has been a move in recent years toward employing molecular tests that use multiplex polymerase chain reaction (PCR) to simultaneously detect multiple pathogens associated with an infectious disease rather than one particular organism. These tests are usually offered as a panel for a particular infectious condition, such as sepsis and blood stream infections or urinary tract 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).

Sepsis Panel

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

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

The T2Bacteria Panel is the first "FDA-cleared test to identify sepsis-causing bacteria directly from whole blood without the wait for blood culture (T2Biosystems, 2019)." This panel is able to identify 50% of all bloodstream infections, 90% of all ESKAPE bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*) pathogens, and 70% of all blood culture species identified in the emergency room with a 95% sensitivity and 98% sensitivity (T2Biosystems, 2019).

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

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

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

Bloodstream Infection Panel

Bloodstream infections or blood infections, also called bacteremia or fungemias, are the presence of bacteria in the blood. Infections in the blood are detected by doing blood cultures. Because of the diversity of organisms detected by different technical platforms, decisions regarding which rapid diagnostic test for bloodstream infections to implement remain challenging. Sepsis is different from bloodstream infections; sepsis is the host response to the bacteria in the blood. Bacteria in the blood can lead to severe health consequences such as sepsis and septic shock. Blood culture is still the gold standard in the diagnosis of bloodstream infections. The authors noted that too many microbiologists still claim that rapid diagnostic is not useful, because studies demonstrating the impact of rapid methods on mortality are rare. (Lamy 2020) (Claeys 2021)

Urinary Tract Infection Panel

Urinary tract infections (UTIs) occur in the urinary system and can be either symptomatic or asymptomatic. UTIs can include cystitis, an infection of the bladder or lower urinary tract, pyelonephritis, an infection of the upper urinary tract or kidney, urosepsis, urethritis, and male-specific conditions, such as bacterial prostatitis and epididymitis (Bonkat et al., 2021; Hooton & Gupta, 2021). Typically, in an infected person, bacteriuria, and pyuria (the presence of pus in the urine) are present and can be present in both symptomatic and asymptomatic UTIs. A urine culture can be performed to determine the presence of bacteria and to characterize the bacterial infection (Meyrier, 2019).

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

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

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

Wound Panel

Wounds (acute or chronic) are almost always colonized by microbes, thereby leading to a significant rate of infection. Panel testing many pathogens have been proposed as a method to quickly identify and therefore treat a wound infection (Armstrong & Meyr, 2021). These panels may be culture-based or nucleic acid-based; nucleic acid panels are typically touted for their speed compared to culture panels.

Firms, such as GenetWorx, Viracor, and MicroGenDX, offer comprehensive panels addressing many different common pathogens, resistance genes, and more. Genera, such as *Streptococcus*, *Enterococcus*, and *Staphylococcus*, are frequent targets of these panels, and many different combinations of panels are available (GenetWorx, 2019; MicroGenDX, 2019b; Viracor, 2019).

The Wounds Pathogen Panel by GenetWorx is able to identify 22 targets including bacteria, fungi, and viruses. Targeted pathogens include *Enterococcus faecalis*, *Methicillin Resistant Staphylococcus aureus* (MRSA), *Methicillin Sensitive Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A Strep), *Streptococcus agalactiae* (Group B Strep), *Streptococcus dysgalactiae* (Group C Strep), *Bacteroides fragilis*, *Bartonella henselae*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bartonella Quintana*, *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida dubliniensis*, *Candida tropicalis*, *Mycobacterium fortuitum*, Herpes Simplex Virus 1, Herpes Simplex Virus 2 and Herpes Simplex Virus 3 (GenetWorx, 2019).

The Viracor Skin and Soft Tissue Infection Panel can identify 19 bacterial targets using TEM-PCR™ (Target Enriched Multiplex Polymerase Chain Reaction). These bacterial targets include *Acinetobacter baumannii*, *Bacteroides spp.*, *Citrobacter freundii*, *Clostridium novyi/septicum*, *Clostridium perfringens*,

Enterobacter aerogenes, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Kingella kingae*, *Klebsiella* spp., *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Staphylococcus aureus*, MRSA- Meth. Resistant *S. aureus*, Panton-Valentine 12eucocidin gene, *Staphylococcus lugdunensis*, *Streptococcus pyogenes* (Group A) and *Pseudomonas aeruginosa* (Viracor, 2019). This test has not been approved by the FDA and has a 2-3 day turnaround time.

Ray, Suaya, and Baxter (2013) described the incidence and microbiology of skin and soft tissue infections (SSTIs). The authors focused on members of a Northern California health plan, identifying 376,262 patients with 471,550 SSTIs. Approximately 23% of these infections were cultured, 54% of these cultures were pathogen-positive, and *Staphylococcus aureus* was found in 81% of these specimens. The researchers calculated the rate of diagnosed SSTIs to be 496 per 10,000 person-years (Ray et al., 2013).

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

Commercial Pathogen Panel Tests		
Type of Panel	Name	Pathogens Identified
Sepsis	T2Bacteria Panel	5 ESKAPE pathogens and potentially more targets
Sepsis	MagiCplex™ Sepsis Real-time Test	90+ including bacteria and fungi
Sepsis	GenMark ePlex® Blood Culture Identification Panel (Gram-positive, Gram-negative and fungal)	Collectively identify 56 bacteria and fungi
Sepsis	BioFire Blood Culture	24 targets including bacteria and yeast
Urinary Tract Infection	NovaDX UTI Test	17 targets including bacteria and yeast
Wound	GenetWorx Wounds Pathogen Panel	22 targets including bacteria, fungi and viruses
Wound	Viracor Skin and Soft Tissue Infection Panel	19 bacterial targets

Summary

Clinical Validity and Utility

SEPSIS

The use of multiplex PCR assays to identify pathogens, following positive blood culture, can be faster than standard techniques involving phenotypic identification and antimicrobial susceptibility testing that is required up to 72 hours after the blood culture became positive (Liesenfeld et al., 2014). A prospective randomized controlled trial evaluating outcomes associated with multiplex PCR detection of bacteria, fungi, and resistance genes directly from positive blood culture bottles concluded that the testing led to more judicious antibiotic use (Banerjee et al., 2015). A study by Ward and colleagues compared the accuracy and speed of organism and resistance gene identification of two commercially available multiplex-PCR sepsis panels to conventional culture-based methods for 173 positive blood cultures. The researchers discovered that both the assays accurately identified organisms and significantly reduced the time to definitive results (on average, between 27.95 and 29.17 hours earlier than conventional method) (Ward et al., 2015). Another study assessed the diagnostic accuracy of a commercially available multiplex

PCR-based assay for detecting infections among patients suspected of sepsis. They concluded that the test had high specificity with a modest sensitivity and had higher rule-in value than the rule-out value. If the patient had a positive result, a clinician can confidently diagnose sepsis and begin appropriate antimicrobial therapy while avoiding unwanted additional testing (Chang et al., 2013).

Bloodstream Infection Panel

The performance characteristics and impact on patient's clinical outcomes of the following technologies were reviewed: multiplex real-time PCR working directly from whole blood (Magicplex Sepsis Real-Time test, Seegene), PCR combined with T2 Magnetic Resonance (T2Candida and T2Bacteria panel, T2Biosystem), and metagenomics-based assays (including SepsiTest, Molzym; iDTECT Dx Blood, PathoQuest; Karius NGS plasma Test, Karius). The authors concluded that the potential of rapid diagnostic tests applied on whole blood for improving the management of patients with bloodstream infection and sepsis is high, both in terms of reducing turnaround times and improving the sensitivity of pathogen and antimicrobial resistance detection. However, there is still limited data on the real-life performance of these tests. Well-designed studies are necessary for assessing the impact of these technologies on patient outcomes. (Peri 2022)

General Screening of Microorganisms: SmartGut™; SmartJane™ ; UroSwab™

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

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

UroSwab is a urine-based proprietary test from Medical Diagnostics LLC. UroSwab is a real-time PCR test intended to detect numerous pathogens—53 different targets as of April 2019—potentially involved in sexually transmitted and urological infections. This test uses a patient's urine, and the turnaround time is estimated at 24-72 hours. The results include whether a pathogen's presence was normal or abnormal and includes comments on what the pathogen's presence means (Diagnostics, 2015a, 2015b).

Guidelines and Recommendations

SEPSIS

Infectious Diseases Society of America (IDSA)

In 2013, the IDSA stated that “molecular diagnostics that detect microbial DNA directly in blood have achieved a modest level of success, but several limitations still exist. Based on available data, well-designed multiplex PCRs appear to have value as sepsis diagnostics when used in conjunction with conventional culture and routine antibiotic susceptibility testing.” **Caliendo et al., 2013; Miller et al., 2018; Shane et al., 2017; Uyeki et al., 2018**

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)

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

Bloodstream Infection

The potential of rapid diagnostic tests applied on whole blood for improving the management of patients with bloodstream infection and sepsis is high, both in terms of reducing turnaround times and improving the sensitivity of pathogen and antimicrobial resistance detection. However, overall, there is still a scarcity of data about the real-life performance of such tests, and well-designed studies are awaited for assessing the impact of these emerging technologies on patient outcomes. (Peri et al 2021)

Wounds

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

Global Wound Biofilm Expert Panel Consensus Guidelines

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

Urinary Tract Infection

The European Association of Urology (EAU)

The EAU published an update to their guidelines on UTIs in 2021. For uncomplicated UTIs (recurrent UTIs, cystitis, pyelonephritis), the EAU does not mention molecular testing at any point of the treatment algorithm; instead, they recommend bacterial culture or dipstick testing for diagnosis and recommending against extensive workup. The EAU notes that antimicrobial susceptibility testing should be performed in all cases of pyelonephritis, but their guidelines do not suggest any methods over another. In complicated UTIs, the EAU recommends urine culture to identify cases of clinically significant bacteriuria (Bonkat et al., 2021).

There is insufficient evidence to support the use of nucleic acid testing for the diagnosis of urinary tract infections, including pyelonephritis, cystitis, prostatitis and orchitis. Urinary tract infections are among the

most common bacterial infections in women. Most urinary tract infections are acute uncomplicated cystitis. A urinalysis, but not urine culture, is recommended in making the diagnosis. Urine cultures are recommended in women with suspected pyelonephritis, women with symptoms that do not resolve or that recur within two to four weeks after completing treatment, and women who present with atypical symptoms (Colgan, 2011, CDC 2017).

The American Urological Association notes that clinicians must document positive urine cultures associated with prior symptomatic episodes. The Clinical Guideline also notes clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with recurrent UTIs. (Anger 2019)

Infectious Disease Society of America

The Infectious Disease Society of America (2018) describes clinical microbiology tests of value in establishing an etiologic diagnosis of infections of the urinary tract, including laboratory procedures for the diagnosis of cystitis, pyelonephritis, prostatitis, epididymitis and orchitis. According to the IDSA, diagnosis of urinary tract infections requires clinical information and physical findings as well as laboratory information. Culture is noted to be appropriate test for the diagnosis of yeast in urine and acute bacterial prostatitis. Rarely, yeast in urine may indicate systemic infection, for which additional tests must be conducted for confirmation (eg, blood cultures and β -glucan levels). Acute bacterial prostatitis is defined by clinical signs and physical findings combined with positive urine or prostate secretion cultures yielding usual urinary tract pathogens. (Miller 2018)

American Urological Association (AUA 2019): Regarding uncomplicated urinary tract infections in women the AUA notes:

- To make a diagnosis of recurrent UTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. (Clinical Principle)
- Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with recurrent UTIs. (Moderate Recommendation; Evidence Level: Grade C)
- Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with recurrent UTIs. (Moderate Recommendation; Evidence Level: Grade C)

(Grade C: Net benefit (or net harm) appears moderate. Applies to most patients in most circumstances but better evidence is likely to change confidence)

Policy History

Date	Action
4/2024	Clarified coding information.
12/2023	New medically necessary and investigational statements for respiratory panels effective 12/1/2023.
10/2023	Clarified coding information.
4/2023	Clarified coding information.
1/2023	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
1/2023	Policy clarified to include the following microorganisms under nucleic acid testing panel: Anaplasma phagocytophilum; Babesia microti; Borrelia miyamotoi; Ehrlichia chaffeensis. References 56-64 added.
9/2022	New medical policy describing: <ul style="list-style-type: none"> • New investigational indications for sepsis panel testing, bloodstream infection panel, panel testing for general screening of microorganisms; and wound panel testing. Effective 9/1/2022. • Ongoing medically necessary indications for nucleic acid testing using amplified probe technique (with or without quantification of viral load) for the following microorganisms: Babesiosis; Ehrlichiosis, unspecified; Tick-borne rickettsiosis, unspecified; transferred from MP #555 Identification of Microorganisms Using Nucleic Acid Probes.

- | | |
|--|---|
| | <ul style="list-style-type: none"> Ongoing investigational indications for urinary tract infection panel. Urinary tract infection panel was transferred from MP #555 Identification of Microorganisms Using Nucleic Acid Probes. |
|--|---|

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Endnotes

¹ Based on expert opinion