2.04.10	Identification of Microorganisms Using Nucleic Acid Probes		
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Section:	2.0 Medicine	Page:	Page 1 of 53

Policy Statement

The use of nucleic acid testing using a direct or amplified probe technique (*without* quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms (see Policy Guidelines):

I. Bartonella henselae or quintana
II. Bordetella pertussis
III. Candida species
IV. Chlamydia pneumoniae
V. Chlamydia trachomatis
VI. Clostridium difficile
VII. Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
VIII. Enterovirus
IX. Herpes simplex virus
X. Human papillomavirus (HPV)
XI. Influenza virus
XII. Legionella pneumophila
XIII. Mumps
XIV. Mycobacterium species
XV. Mycobacterium tuberculosis
XVI. Mycobacterium avium-intracellulare
XVII. Mycoplasma pneumoniae
XVIII. Neisseria gonorrhoeae
XIX. Rubeola (measles)
XX. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
XXI. Staphylococcus aureus
XXII. Staphylococcus aureus, methicillin-resistant
XXIII. Streptococcus, group A
XXIV. Streptococcus, group B
XXV. Trichomonas vaginalis
XXVI. Zika virus

The use of nucleic acid testing using a direct or amplified probe technique (with or without quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms:

I. Cytomegalovirus
II. Hepatitis B virus
III. Hepatitis C virus
IV. Human herpesvirus 6
V. Human Immunodeficiency Virus 1 (HIV-1)
VI. Human Immunodeficiency Virus 2 (HIV-2)

The use of nucleic acid testing with quantification of viral load is considered **investigational** for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered medically necessary.

The use of nucleic acid testing using a direct or amplified probe technique is considered **investigational** for the following microorganisms:

I. Gardnernella vaginalis
II. Hepatitis G

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The use of the following nucleic acid testing panel (*without* quantification of viral load) may be considered **medically necessary**:

I. Respiratory Virus Panel

The use of the following nucleic acid testing panels (*with or without* quantification of viral load for viral panel elements) is considered **investigational**:

I. Central nervous system pathogen panel
II. Gastrointestinal pathogen panel

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The use of molecular diagnostics for the diagnosis and management of *Borrelia burgdorferi* infection (Lyme disease) is addressed in Blue Shield of California Medical Policy: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease.

It should be noted that the technique for quantification includes both amplification and direct probes; therefore, simultaneous coding for both quantification with either amplification or direct probes is not warranted.

Antibiotic sensitivity of streptococcus A cultures is generally not performed for throat cultures. However, if an antibiotic sensitivity is considered, then the most efficient method of diagnosis would be a combined culture and antibiotic sensitivity.

For *Candida* species, culture for yeast remains the criterion standard for identifying and differentiating these organisms. Although sensitivity and specificity are higher for NAATs than for standard testing methods, the CDC and other association guidelines do not recommend NAATs as first-line testing for *Candida* species. The CDC Centers for Disease Control and Prevention (2015) classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or, in nonimmunocompromised women, as likely to be caused by *C. albicans*. A presumptive diagnosis can be made in the clinical care setting. However, for complicated infections, the CDC states that NAATs may be necessary to test for multiple *Candida* subspecies. Complicated vulvovaginal candidiasis is classified as being recurrent or severe; or, in women with uncontrolled diabetes, debilitation, or immunosuppression, as less likely to be caused by a *C. albicans* species.

In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared with traditional culture techniques is the rapidity of results. This advantage suggests that the most appropriate use of the DNA probe technique is in the setting of impending labor, for which prompt results could permit the initiation of intrapartum antibiotic therapy.

Use of NAAT for SARS-CoV-2 is for confirming Coronavirus Disease 2019 (COVID-19) diagnoses. This medical policy does not address antibody testing (serological IgG assays).

Many probes have been combined into panels of tests. For the purposes of this policy, other than the respiratory pathogen panel, gastrointestinal pathogen panel and, central nervous system panel, only individual probes are reviewed.

Coding

There is a CPT PLA code that represents the MYCODART Dual Amplification Real Time PCR Panel:

- **0068U**: Candida species panel (C. albicans, C. glabrata, C. parapsilosis, C. kruseii, C tropicalis, and C. auric), amplified probe technique with qualitative report of the presence or absence of each species

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There is a CPT PLA code that represents the MYCODART Dual Amplification Real Time PCR Panel for 4 Aspergillus species:

- **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

There is a CPT PLA code that represents the MicroGenDX qPCR & NGS analysis for infection:

- **0112U**: Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene

There is a CPT PLA code that represents the GenMark Diagnostics ePlex® Respiratory Pathogen (RP) Panel:

- **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

There is a CPT PLA code that represents the GenMark Diagnostics ePlex® BCID Fungal Pathogens Panel:

- **0140U**: Infectious disease (fungi), fungal pathogen identification, DNA (15 fungal targets), blood culture, amplified probe technique, each target reported as detected or not detected

There are CPT PLA codes that represent the GenMark Diagnostics ePlex® BCID Gram-Positive Panel:

- **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

There is a CPT PLA code that represents the BioFire® Diagnostics BioFire® FilmArray® Pneumonia Panel:

- **0151U**: Infectious disease (bacterial or viral respiratory tract infection), pathogen specific nucleic acid (DNA or RNA), 33 targets, real-time semi-quantitative PCR, bronchoalveolar lavage, sputum, or endotracheal aspirate, detection of 33 organismal and antibiotic resistance genes with limited semi-quantitative results

There is a CPT code that was developed to distinguish Mycoplasma genitalium from other types of sexually transmitted infections. This service may have been previously billed with CPT code 87798:

- **87563**: Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma genitalium, amplified probe technique

The following CPT code may be used for gastrointestinal (GI) pathogen panel:

- **0097U**: Gastrointestinal pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 22 targets (Campylobacter [C. jejuni/C. coli/C. upsaliensis], Clostridium difficile [C. difficile] toxin A/B, Plesiomonas shigelloides, Salmonella, Vibrio [V. parahaemolyticus/V. vulnificus/V. cholerae], including specific identification of Vibrio cholerae, Yersinia enterocolitica, Enteroaggregative Escherichia coli [EAEC], Enteropathogenic Escherichia coli [EPEC], Enterotoxigenic Escherichia coli [ETEC] lt/st, Shiga-like toxin-producing Escherichia coli [STEC] stx1/stx2 [including specific identification of the E. coli O157 serogroup within STEC], Shigella/Enteroinvasive

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Escherichia coli [EIEC], Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia [also known as G. intestinalis and G. duodenalis], adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, sapovirus [Genogroups I, II, IV, and V])

Effective January 1, 2021, there are two new MAAA codes for bacterial vaginosis testing from vaginal fluid specimens:

- **81513**: Infectious disease, bacterial vaginosis, quantitative real-time amplification of RNA markers for Atopobium vaginae, Gardnerella vaginalis, and Lactobacillus species, utilizing vaginal-fluid specimens, algorithm reported as a positive or negative result for bacterial vaginosis
- **81514**: Infectious disease, bacterial vaginosis and vaginitis, quant real-time amp of DNA markers for Gardnerella vaginalis, Atopobium vaginae, Megasphaera type 1, Bacterial Vaginosis Assoc Bacteria-2 (BVAB-2), and Lactobacillus species

Effective January 1, 2021, there is a new MAAA code for Envisia® Genomic Classifier, by Veracyte, Inc. Per the manufacturer, the test predicts positive or negative usual interstitial pneumonia in patients with interstitial lung disease.

- **81554**: Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (e.g., positive or negative for high probability of usual interstitial pneumonia [UIP])

Table PG1 provides a list of CPT codes for various nucleic acid probes.

Table PG1. CPT Codes for Nucleic Acid Probes

Pathogen	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or quintana		87471	87472
Candida species	87480	87481	87482
Chlamydophila pneumoniae	87485	87486	87487
Chlamydia trachomatis	87490	87491	87492
Clostridium difficile	87493		
Cytomegalovirus	87495	87496	87497
Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)		87500	
Enterovirus		87498	
Gardnerella vaginalis	87510	87511	87512
Gastrointestinal pathogen panel		87505-87507	
Central nervous system pathogen panel	87483 effective 01/01/17		
Hepatitis B virus		87516	87517
Hepatitis C virus	87520	87521	87522
Hepatitis G virus	87525	87526	87527
Herpes simplex virus	87528	87529	87530
Herpes virus-6	87531	87532	87533
HIV-1	87534	87535	87536
HIV-2	87537	87538	87539
Human papillomavirus		87623-87625	
Influenza virus		87501-87503	
Legionella pneumophila	87540	87541	87542
Mycobacteria species	87550	87551	87552
Mycobacterium tuberculosis	87555	87556	87557
Mycobacterium avium-intracellulare	87560	87561	87562

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Pathogen	Direct Probe	Amplified Probe	Quantification
Mycoplasma pneumoniae	87580	87581	87582
Neisseria gonorrhoeae	87590	87591	87592
Respiratory virus panel		87631-87633	
Staphylococcus aureus		87640	
Staphylococcus aureus, methicillin-resistant		87641	
Streptococcus, group A	87650	87651	87652
Streptococcus, group B		87653	
Trichomonas vaginalis	87660	87661	

[a] Blue Shield of California Medical Policy: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease.

CPT codes 87797, 87798, and 87799 describe the use of direct probe, amplified probe, and quantification, respectively, for infectious agents not otherwise specified. A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy.

Description

Nucleic acid probes are available for the identification of a wide variety of microorganisms. Nucleic acid probes can also be used to quantitate the number of microorganisms present. This technology offers advantages over standard techniques when rapid identification is clinically important when microbial identification using standard culture is difficult or impossible, and/or when treatment decisions are based on quantitative results.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

A list of current U.S. Food and Drug Administration-approved or cleared nucleic acid-based microbial tests is available online.[3,] Table 1 lists tests approved or cleared by the Food and Drug Administration that do not have specific CPT codes.

Table 1. FDA-Approved/Cleared Tests Without CPT Codes

FDA-Approved/Cleared Diagnostic Test	Test Type
Bacillus anthracis	Real-time PCR
Coxiella burnetii (Q fever)	Real-time PCR
Enterococcus faecalis	PNA FISH
Escherichia coli and Pseudomonas aeruginosa	PNA FISH

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FDA-Approved/Cleared Diagnostic Test	Test Type
Escherichia coli and/or Klebsiella pneumoniae and Pseudomonas aeruginosa	PNA FISH
Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa	PNA FISH
Francisella tularensis	Real-time PCR
Leishmania	Real-time PCR
Yersinia pestis	Real-time PCR
Adenovirus	Multiplex real-time RT-PCR
Avian flu	Real-time RT-PCR
Human metapneumovirus	Multiplex real-time RT-PCR
Influenza virus A/H5	Real-time RT-PCR
Influenza virus H1N1	Real-time RT-PCR
Dengue virus	Real-time RT-PCR
Gram-positive/gram-negative bacteria panel	Multiplex nucleic acid amplification

FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; PCR: polymerase chain reaction; PNA: peptide nucleic acid; RT: reverse transcriptase.

Rationale

Background

Microorganisms and Clinical Disease

Various bacteria, viruses, and fungi that can cause clinical disease and can be detected with various nucleic acid probe techniques are briefly outlined below.

Bartonella henselae or quintana

Bartonella henselae is responsible for the cat-scratch disease. In most patients (90%-95%), the infection is a localized skin and lymph node disorder that occurs close to the site of inoculation and is characterized by chronic regional lymphadenopathy that develops about 2 weeks after contact with a cat. Less commonly, Bartonella henselae infection may lead to disseminated infection, which can manifest as visceral organ involvement, often with fever and hepatosplenomegaly, a variety of ocular manifestations, and neurological manifestations (most commonly, encephalopathy).

Bartonella may also cause an opportunistic infection in HIV-infected patients, in whom it is characterized by an acute febrile bacteremic illness, evolving to an asymptomatic bacteremia and finally indolent vascular skin lesions. The organism is typically detected using culture techniques, although an incubation period of 5 to more than 30 days is required. DNA probe technology has been investigated as a diagnostic technique.

Bartonella quintana has classically been associated with “trench fever,” which is characterized by systemic symptoms (bone pain, malaise, headache), along with recurring fevers of varying durations. Among HIV-infected patients, B. quintana has been associated with bacillary angiomatosis.

Bartonella are fastidious organisms, making culture difficult. Histology of lesions affected by bacillary angiomatosis may be characteristic. Histology of affected lymph nodes or other tissue with B. henselae may demonstrate findings that are suggestive of cat-scratch disease, but which may be seen in other conditions. Two antigenic methods are available, one using indirect fluorescence assay and one using enzyme immunosorbent assay, for both B. henselae and B. quintana infections. A positive serologic test is generally considered supportive, but not definitive, for Bartonella infection. Serologic methods may have limited yield in immunosuppressed patients.

Candida Species

A commonly occurring yeast, Candida species normally can be found on the diseased skin, throughout the entire gastrointestinal tract, expectorated sputum, the female genitalia, and in

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the urine of patients with indwelling Foley catheters. Clinically significant Candida infections are typically diagnosed by clinical observation or by identification of the yeast forms on biopsy specimens. Candida species are a common cause of vaginitis.

Chlamydophila pneumoniae
Chlamydophila pneumoniae is an important cause of pneumonia, bronchitis, and sinusitis. Culture and isolation of the microorganism are difficult; a micro-immunofluorescence serum test may be used. The use of polymerase chain reaction amplification now offers a rapid diagnosis.

Chlamydia trachomatis
Chlamydia trachomatis is a significant intracellular pathogen causing, most prominently, urogenital disease (including pelvic inflammatory disease) and perinatal infections.

C. trachomatis is also responsible for lymphogranuloma venereum. Due to its prevalence and association with pelvic inflammatory disease and perinatal disease, widespread testing of chlamydia is recommended; routine chlamydia testing has been adopted as a quality measure by Healthcare Effectiveness Data and Information Set. This microorganism can be diagnosed by (1) identifying the typical intracytoplasmic inclusions in cytology specimens; (2) isolation in tissue culture; (3) demonstration of chlamydial antigen by enzyme-linked immunosorbent assay or by immunofluorescent staining; or (4) demonstration of DNA using a direct probe or amplification technique.

Cytomegalovirus
Cytomegalovirus (CMV) is a common virus, but rarely causes clinical disease in healthy individuals. However, this virus can cause protean disease syndromes, most prominently in immunosuppressed patients, including transplant recipients or those infected with HIV. CMV can also remain latent in tissues after recovery of the host from an acute infection. Diagnosis depends on the demonstration of the virus or viral components or demonstration of a serologic rise. DNA probe techniques, including amplification, have also been used to identify patients at-risk of developing CMV disease as a technique to triage antiviral therapy.

Clostridium difficile
Clostridium difficile is an anaerobic, toxin-producing bacteria present in the intestinal tract. It causes clinical colitis when the normal intestinal flora is altered, and overgrowth of C. difficile occurs. The common precipitant that disrupts the normal intestinal flora is previous treatment with antibiotics. The disorder has varying severity but can be severe and in extreme cases, life-threatening. C. difficile is easily spread by person-to-person contact and is a common cause of hospital-acquired outbreaks. Hospital infection-control measures, such as wearing gloves and handwashing with soap and water, are effective methods of reducing the spread of C. difficile. The standard diagnosis is made by an assay for the C. difficile cytotoxin or by routine culture methods.

Enterovirus
Enteroviruses are single-stranded RNA viruses. This group of viruses includes the polioviruses, coxsackieviruses, echoviruses, and other enteroviruses. In addition to 3 polioviruses, there are more than 60 types of nonpolio enteroviruses that can cause disease in humans. Most people who are infected with a nonpolio enterovirus have no disease symptoms. Infected persons who develop illness usually develop either mild upper respiratory symptoms, flu-like symptoms with fever and muscle aches, or an illness with rash. Less commonly, enteroviruses can cause "aseptic" or viral meningitis, encephalitis, acute paralysis, and/or myocarditis. Enteroviral infections can cause life-threatening systemic infections in neonates, which are often associated with myocarditis or fulminant hepatitis. The use of amplified probe DNA test(s) can be used to detect enteroviruses.

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Gardnerella vaginalis
A common microorganism, Gardnerella vaginalis is typically found in the human vagina and is usually asymptomatic. However, G. vaginalis is found in virtually all women with bacterial vaginosis and is characterized by inflammation and perivaginal irritation. The microorganism is typically identified by culture. The role of G. vaginalis in premature rupture of membranes and preterm labor is also under investigation.

Hepatitis B, C, and G
Hepatitis is typically diagnosed by a pattern of antigen and antibody positivity. However, the use of probe technology permits the direct identification of hepatitis DNA or RNA, which may also provide prognostic information. Quantification techniques are used to monitor the response to direct-acting antiviral, interferon, and/or ribavirin therapy in patients with hepatitis C.

Herpes Simplex Virus
Herpes simplex infection of the skin and mucous membranes is characterized by a thin-walled vesicle on an inflammatory base typically in the perioral, ocular, or genital area, although any skin site may be involved. The diagnosis may depend on a pathologic examination of cells scraped from a vesicle base or by tissue culture techniques. Herpes simplex encephalitis is one of the most common and serious sporadic encephalitides in immunocompetent adults. The polymerase chain reaction technique to detect herpes simplex virus in the cerebrospinal fluid has been used to provide a rapid diagnosis of herpes virus encephalitis.

Human Herpesvirus 6
Human herpesvirus 6 (HHV-6) is the common collective name for HHV-6A and HHV-6B. These closely related viruses are 2 of the 9 herpesviruses known to have humans as their primary host. HHV-6 is widespread in the general population. In immunocompetent hosts, HHV-6 primary infection typically causes a mild, self-limited illness in childhood, often roseola. HHV-6 may also cause meningitis and encephalitis in children and adults. Diagnosis is typically based on rising serologic titers.

In immunosuppressed patients, HHV-6 reactivation may cause meningitis, encephalitis, pneumonitis, and/or bone marrow suppression.[1,]

HIV-1 and HIV-2
DNA probe technology for HIV-1 is widely disseminated, and HIV-1 quantification has become a standard laboratory test in HIV-1 infected patients. HIV-2 can result in severe immunosuppression and the development of serious opportunistic diseases. Although HIV-2 has been reported in the United States, it is most commonly found in Western Africa. Blood donations are routinely tested for HIV-2, but due to its rarity in this country, clinical testing for HIV-2 is typically limited to those in contact with persons in a country where HIV-2 is endemic or when the clinical picture suggests HIV infection, but testing for HIV-1 is negative.

Influenza Virus
Influenza virus is a very common pathogen that accounts for a high burden of morbidity and mortality, especially in elderly and immunocompromised patients. The most common means of identifying influenza is by viral culture, which takes 48 to 72 hours to complete. Influenza is highly contagious and has been the etiology of numerous epidemics and pandemics. Identification of outbreaks is important so that isolation measures may be undertaken to control the spread of disease. Antiviral treatment can be effective if instituted early in the course of the disease. Therefore, rapid identification of influenza virus is important in making treatment decisions for high-risk patients and in instituting infection-control practices.

Legionella pneumophila
Legionella pneumophila is among the most common microbial etiologies of community-acquired pneumonia. Laboratory diagnosis depends on culture, direct fluorescent antibody

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tests, urinary antigens, or DNA probe. DNA probe techniques have also been used in epidemiologic investigations to identify the source of a Legionella outbreak.

Mycobacteria Species
Although mycobacterium can be directly identified in sputum samples (i.e., acid-fast bacilli), these organisms may take 9 to 16 days to culture. DNA probes have also been used to identify specific mycobacterial groups (i.e., mycobacterial tuberculosis, avian complex, intracellulare) after culture. Also, amplification techniques for Mycobacterium tuberculosis may be used in patients who have a positive smear. The rapid identification of M. tuberculosis permits prompt isolation of the patient and identification of the patient's contacts for further testing.

Mycoplasma pneumoniae
Mycoplasma pneumoniae is an atypical bacterium that is a common cause of pneumonia. It is most prevalent in younger patients below age 40 years and in individuals who live or work in crowded areas such as schools or medical facilities. The infection is generally responsive to antibiotics of the macrolide or quinolone class. Most patients with M. pneumonia recover completely, although the course is sometimes prolonged for up to 4 weeks or more. Extrapulmonary complications of M. pneumonia occur uncommonly, including hemolytic anemia and the rash of erythema multiforme.

Neisseria gonorrhoeae
Isolation by culture is the conventional form of diagnosis for this common pathogen, but culture requires specific sampling and plating techniques. Direct DNA probes and amplification techniques have also been used. Neisseria is often tested for at the same time as chlamydia.

Papillomavirus
Papillomavirus species are common pathogens that produce epithelial tumors of the skin and mucous membranes, most prominently the genital tract. Physical examination is the first diagnostic technique. Direct probe and amplification procedures have been actively investigated in the setting of cervical lesions. The ViraPap test is an example of a commercially available direct probe technique for identifying papillomavirus. There has been interest in evaluating the use of viral load tests of human papillomavirus to identify patients at highest risk of progressing to invasive cervical carcinoma.

Streptococcus, Group A
Also referred to as Streptococcus pyogenes, this pathogen is the most frequent cause of acute bacterial pharyngitis. It can also give rise to a variety of cutaneous and systemic conditions, including rheumatic fever and post-streptococcal glomerulonephritis. A throat culture is the preferred method for diagnosing streptococcal pharyngitis. Also, a variety of commercial kits are now available that use antibodies for the rapid detection of group A carbohydrate antigen directly from throat swabs. While very specific, these kits are less sensitive than throat cultures so that a negative test may require confirmation from a subsequent throat culture. DNA probes have also been used for direct identification of streptococcus and can be used as an alternative to a throat culture as a back-up test to a rapid, office-based strep test.

Streptococcus, Group B
Also referred to as Streptococcus agalactiae, group B streptococcus (GBS), is the most common cause of sepsis, meningitis, or death among newborns. Early-onset disease, within 7 days of birth, is related to exposure to GBS colonizing the mother's anogenital tract during birth. The Centers for Disease Control and Prevention have recommended either maternal risk assessment or screening for GBS in the perinatal period.[2,] Screening consists of obtaining vaginal and anal specimens for culture at 35 to 37 weeks of gestation. The conventional culture and identification process requires 48 hours. Therefore there has been great interest in developing rapid assays using DNA probes to shorten the screening process so that screening could be performed in the intrapartum period with the institution of antibiotics during labor.

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Trichomonas vaginalis

Trichomonas is a single-cell protozoan that is a common cause of vaginitis. The organism is sexually transmitted and can infect the urethra or vagina. The most common way of diagnosing Trichomonas is by clinical signs and by directly visualizing the organism by microscopy in a wet prep vaginal smear. The culture of Trichomonas is limited by poor sensitivity. Treatment with metronidazole results in a high rate of eradication. The disease is usually self-limited without sequelae, although infection has been associated with premature birth and higher rates of HIV transmission, cervical cancer, and prostate cancer.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. The evidence review section of this policy update focuses on pathogen panels. The supplemental information section contains supporting information for the medical necessity of the use of the organism-specific nucleic acid amplification tests (NAATs) which have guideline support. Guidelines from the Centers for Disease Control and Prevention, National Institute of Health, Infectious Disease Society of America or America Academy of Pediatrics were used to evaluate appropriate indications for the following individual microorganisms; *Bartonella henselae or Quintana*, *Candid Species*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium difficile*, *Cytomegolovirus*, *Enterovirus*, *Hepatitis B*, *Hepatitis C*, *Herpes Simplex Virus*, *Human Herpesvirus 6*, *Human Papillomavirus*, *HIV 1*, *Influenza virus*, *Legionella pneumophila*, *Mycobacteria Species*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Streptococcus* Group A and Group B, and *Vancomycin-resistant enterococcus*, Zika virus.

Central Nervous System Bacterial and Viral Panel

Clinical Context and Test Purpose

The purpose of nucleic acid-based central nervous system (CNS) pathogen panels is to provide a diagnostic option that is an alternative to or an improvement on existing tests for patients with signs and/or symptoms of meningitis and/or encephalitis.

The question addressed in this evidence review is: Does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with suspected meningitis and/or encephalitis?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with signs and/or symptoms of meningitis and/or encephalitis.

Interventions

The therapy being considered is nucleic acid-based CNS pathogen panel.
Patients with signs and/or symptoms of meningitis and/or encephalitis are managed by infectious disease specialists and emergency medicine professionals in an emergency or inpatient clinical setting. Testing with a CNS pathogen panel leads to reduced time to diagnosis compared with standard laboratory techniques (approximately 1-8 hours).[1,]

Comparators

Comparators of interest include no CNS pathogen-specific testing and culture or nucleic acid-based testing for individual pathogens.

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Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, necessity for additional testing, and delay of correct diagnosis and treatment.

Though not completely standardized, follow-up for suspected meningitis and/or encephalitis would typically occur in the days to weeks after a diagnosis decision and initiation of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic [ROC], area under receiver operating characteristic [AUROC], c-statistic, likelihood ratios) may be included but are less informative.
- Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

The standard approach to the diagnosis of meningitis and encephalitis is culture and pathogen-specific polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF) based on clinical characteristics. These techniques have a slow turnaround time, which can delay administration of effective therapies and lead to unnecessary empirical administration of broad-spectrum antimicrobials.

The FilmArray Meningitis/Encephalitis (ME) Panel (BioFire Diagnostics, Salt Lake City, UT) is a nucleic acid-based test that simultaneously detects multiple bacterial, viral, and yeast nucleic acids from CSF specimens obtained via lumbar puncture from patients with signs and/or symptoms of meningitis and/or encephalitis. The test has been cleared for marketing through the U.S. Food and Drug Administration (FDA) 510(k) process. The test identifies 14 common organisms responsible for community-acquired meningitis or encephalitis:

Bacteria: *Escherichia coli K1*; *Haemophilus influenzae*; *Listeria monocytogenes*; *Neisseria meningitides*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*;

Viruses: Cytomegalovirus; Enterovirus; Herpes simplex virus 1; Herpes simplex virus 2; Human herpesvirus 6; Human parechovirus; Varicella zoster virus;

Yeast: *Cryptococcus neoformans/gattii*.
Run-time is approximately 1 hour per specimen.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and

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unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The systematic review and meta-analysis by Tansarli and Chapin (2019) examined the diagnostic accuracy of the BioFire FilmArray ME panel. [2] Thirteen prospective and retrospective studies conducted from 2016 through 2019 were reviewed (N=3764 patients); 8 were included in the meta-analysis (n=3059 patients). Included in the meta-analysis is the study by Leber et al [2016][3], which is discussed below. Risk of bias among the studies was mixed but tended toward low-risk, with the index test aspect being most questionable. No applicability concerns were found in any studies. To be eligible, studies had to provide sensitivity and specificity data compared with a reference standard. Patients in the studies had infections caused by a variety of components found on the panel (bacterial, viral, *Cryptococcus neoformans/gatti*). Table 2 summarizes the sensitivity, specificity, and other measurements of accuracy. The highest proportions of false-positive results were for *Streptococcus pneumoniae* (17.5%) and *Streptococcus agalactiae* (15.4%). The highest proportion of false negatives was seen for Herpes Simplex Virus 1 and 2, *Enterovirus*, and *C. neoformans/gatti*. The rate of false-positive results with the ME panel suggests this method should be used with caution, and additional diagnostic methods should be used to confirm panel results.

Table 2. Accuracy of BioFire FilmArray Meningitis/Encephalitis Panel

Measurement	Sensitive, Mean %	Specificity, Mean	PPV %	NPV %	False-Positive Results Before and After Adjudication,[a] %		False-Negative Results Before and After Adjudication, %	
					Before	After	Before	After
Value	90.2	97.7	85.1	98.7	11.4	4.0	2.2	1.5
95% CI	86.2–93.1	94.6–99.0	NR	NR	NR	NR	NR	NR
Range	60–100	88–100	NR	NR	NR	NR	NR	NR

Source: Tansarli and Chapin (2019)[2]
CI: confidence interval; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] Adjudication is further investigation of results, which could include further testing, clinician input, or chart review. In this study, it was performed for discordant results between index and reference tests.

The study by Leber et al. (2016) was the FDA pivotal study, as well as the largest and one of the only prospective studies available.[3] A total of 1560 samples were tested, which were taken from children and adults with available CSF but not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis. (See Table 3 for study characteristics.) Even the most prevalent organisms were present only a small number of times in the samples. The specificities ranged from 98% to 100% and, given the high number of true negatives, the specificities were estimated with tight precision. However, given the small number of true positives, the sensitivities to detect any given organism could not be estimated with precision. A total of 141 pathogens were detected in 136 samples with the FilmArray and 104 pathogens were detected using comparator methods; 43 FilmArray results were false-positive compared with the comparator method and 6 were false-negative. For 21 of the 43 false-positives, repeat testing of the FilmArray, comparator, or additional molecular testing supported the FilmArray results. The remaining 22 false-positives (16% of all positives) were unresolved. Codetections were observed in 3.7% (5/136) positive specimens. All 5 included a bacterial and viral positive result, and all 5 specimens were found to have a false-positive result demonstrated by comparator testing. (See Table 4 for detailed clinical validity data.) The investigators suggested that the discrepancies could have been due to specimen contamination or another problem with the assay configuration or testing process.

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The smaller studies[4,5] were consistent with Leber (2016) in estimating the specificities for all included pathogens to be greater than 98%. However, there were also a very low number of true-positives for most pathogens in these studies and thus the estimates of sensitivities were imprecise. Relevance, study design, and trial conduct limitations are shown in Tables 5 and 6.

Table 3. Characteristics of Clinical Validity Studies of Central Nervous System Panel

Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Leber et al. (2016)[3]	Children and adults from whom a CSF specimen was available from standard care testing for bacterial culture; not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis	Nonconcurrent prospective	Culture and PCR	Processed within 7 days of collection or immediately frozen for future testing	Yes
Hanson et al. (2016)[5]	Children and adults from whom a CSF specimen was available who had been tested with at least 1 conventional method	Retrospective, selection method not clear	Culture and PCR with discrepancy resolution LDT PCR	Stored up to 2 y after collection	Yes
Graf et al. (2017)[4]	Positive samples (children) selected based on positivity of reference method for any of targets on the CNS panel. Negative samples selected based on negativity of reference sample and with preference for samples highly suggestive of meningitis or encephalitis	Retrospective, convenience	Culture and PCR	Stored up to 2 y after collection	NR

CNS: central nervous system; CSF: cerebrospinal fluid; LDT: laboratory-developed test; NR: not reported; PCR: polymerase chain reaction.

Table 4. Results of Clinical Validity Studies of Central Nervous System Panel

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/ Positive % Agreement	Specificity/ Negative % Agreement
Leber et al. (2016)[3]	1643	1560	Insufficient volume, outside the 7-d window, repeat subject, or invalid FilmArray test.			
Bacteria						
Escherichia coli K1				0.1	100 (34 to 100)	99.9 (99.6 to 100)
Haemophilus influenzae				0.06	100 (NA)	99.9 (99.6 to 100)
Listeria monocytogenes				0		100 (99.8 to 100)
Neisseria meningitides				0		100 (99.8 to 100)
Streptococcus agalactiae				0.06	0 (NA)	99.9 (99.6 to 100)
Streptococcus pneumoniae				0.3	100 (51 to 100)	99.2 (98.7 to 99.6)
Viruses						

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Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
Cytomegalovirus				0.2	100 (44 to 100)	99.8 (99.4 to 99.9)
Enterovirus				2.9	96 (86 to 99)	99.5 (99.0 to 99.8)
Herpes simplex virus 1				0.1	100 (34 to 100)	99.9 (99.5 to 100)
Herpes simplex virus 2				0.6	100 (72 to 100)	99.9 (99.5 to 100)
Human herpesvirus 6				1.3	86 (65 to 95)	99.7 (99.3 to 99.9)
Human parechovirus				0.6	100 (70 to 100)	99.8 (99.4 to 99.9)
Varicella zoster virus				0.3	100 (51 to 100)	99.8 (99.4 to 99.9)
Yeast						
Cryptococcus neoformans/Cryptococcus gattii				0.06	100 (NA)	99.7 (99.3 to 99.9)
Hanson et al. (2016)[5]	342	342	NR			
Bacteria						
Escherichia coli K1				0.3	100 (3 to 100)	100 (98 to 100)
Haemophilus influenza				1.5	100 (48 to 100)	100 (97 to 100)
Listeria monocytogenes				0	NA	100 (98 to 100)
Neisseria meningitides				0.3	100 (3 to 100)	100 (98 to 100)
Streptococcus agalactiae				0.9	67 (9 to 99)	99 (95 to 100)
Streptococcus pneumoniae				1.5	100 (48 to 100)	99 (96 to 100)
Viruses						
Cytomegalovirus				2.0	57 (18 to 90)	100 (91 to 100)
Enterovirus				11.1	97 (86 to 100)	100 (69 to 100)
Herpes simplex virus 1				3.5	93 (66 to 100)	98 (89 to 100)
Herpes simplex virus 2				8.5	100 (88 to 100)	100 (82 to 100)
Human herpesvirus 6				5.6	95 (74 to 100)	100 (93 to 100)
Human parechovirus				0.3	100 (3 to 100)	100 (93 to 100)
Varicella zostervirus				9.4	100 (89 to 100)	100 (79 to 100)
Yeast						
Cryptococcus neoformans/Cryptococcus gattii				2.6	64 (35 to 87)	NA
Graf et al (2017)[4]	133	133	NR			
Bacteria						
Haemophilus influenzae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus agalactiae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus pneumoniae				NA[a]	100 (28 to 100)[b]	100 (96 to 100)[b]
Viruses						
Enterovirus				NA[a]	95 (82 to 99)[b]	100 (94 to 100)[b]

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Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
Herpes simplex virus 1				NA[a]	50 (7 to 93)[b]	100 (96 to 100)[b]
Herpes simplex virus 2				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Human herpesvirus 6				NA[a]	100 (9 to 100)[b]	100 (96 to 100)[b]
Human parechovirus				NA[a]	94 (70 to 100)[b]	100 (95 to 100)[b]

CI: confidence interval; CNS: central nervous system; NA: not available; NR: not reported.
a Positives and negatives retrospectively selected from a convenience sample with different selection criteria; prevalence is unknown.
b Confidence intervals not provided in publication; estimated based on available information.
The purpose of the limitations tables (see Tables 5 and 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 5. Study Relevance Limitations of Studies of Central Nervous System Panels

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Leber et al. (2016)[3.]	4. Participants not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis	3. Used investigational version of test but varies from marketed version only in that Epstein-Barr virus is not available in the marketed version			
Hanson et al. (2016)[5.]	3. Selection criteria with respect to clinical characteristics not described	3. Used investigational version (see above)			
Graf et al. (2017)[4.]	4. Selection criteria varied for positive and negative samples				
Key	1.Intended use population unclear 2.Clinical context for test is unclear 3.Study population unclear 4.Study population not representative of intended clinical use 5.Study population is subpopulation of intended use	1.Classification thresholds not defined 2.Version used unclear 3.Not version currently in clinical use	1.Classification thresholds not defined 2.Not compared with credible reference standard 3.Not compared with other tests in use for same purpose	1.Study does not directly assess a key health outcome 2.Evidence chain or decision model not explicated 3.Key clinical validity outcomes not reported (sensitivity, specificity, predictive values) 4.Reclassification of diagnostic or risk categories not reported 5.Adverse events of the test not	1.Follow-up duration not sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determined)

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
				described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)	

CNS: central nervous system; FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest (e.g., older version of test, not applied as intended).
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (see template Results tables; 4. Reclassification of diagnostic or prognostic risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Leber et al. (2016)[3]			2.Many tests performed on frozen samples			
Hanson et al. (2016)[5]	1. Not clear if participants were consecutive		2. Many tests performed on frozen samples		1. Not clear if there were indeterminate samples	
Graf et al. (2017)[4]	3.Selection not random or consecutive and varied for positive and negatives	1. Not clear if blinded	2.Many tests performed on frozen samples		1.Not clear if there were indeterminate samples	1. Confidence intervals not provided
Key	1.Selection not described 2.Selection not random nor consecutive (ie, convenience)	1.Not blinded to results of reference or other comparator tests	1.Timing of delivery of index or reference test not described 2.Timing of index and comparator tests not same 3.Procedure for interpreting tests not described 4.Expertise	1.Not registered 2.Evidence of selective reporting 3.Evidence of selective publication	1.Inadequate description of indeterminate and missing samples 2.High number of samples excluded 3.High loss to follow-up or missing data	1.Confidence intervals and/or p values not reported 2.No statistical test reported to compare with alternatives

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Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
			of evaluators not described			

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported; 3: Insufficient consideration of potential confounding.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Central Nervous System Bacterial and Viral Panel
The FilmArray ME Panel provides fast diagnoses compared with standard culture and pathogen-specific PCR, and because it combines multiple individual nucleic acid tests, clinicians can test for several potential pathogens simultaneously. The test uses only a small amount of CSF, leaving remaining fluid for additional testing if needed. The test is highly specific for the included organisms. However, due to the low prevalence of these pathogens overall, the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest study were reported to be false-positives, which could cause harm if used to make clinical decisions. Also, a negative panel result does not exclude infection due to pathogens not included in the panel.

Gastrointestinal Pathogen Panel
Clinical Context and Test Purpose
The purpose of nucleic acid-based gastrointestinal (GI) pathogen panels is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with signs and/or symptoms of GI conditions.

The question addressed in this evidence review is: Does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with suspected GI infections?

The following PICO was used to select literature to inform this review.

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Patients
The relevant population of interest is individuals with signs and/or symptoms of gastroenteritis and GI conditions.
The most common 2 types of GI pathogens are either bacterial or viral, including but not limited to the following[6,7,8,]:

- Bacterial (common to U.S. and may be foodborne): *Bacillus cereus*, *Campylobacter*, *Clostridium difficile*, *Clostridium botulinum*, *Clostridium perfringens*, *Cronobacter sakazakii*, *Esherichia coli*, *Listeria monocytogenes*, *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, *Yersinia enterocolitica*
- Viral: norovirus, rotavirus, adenovirus, astrovirus, sapovirus

Norovirus is the most common cause of foodborne illness in the U.S.[9,]

Interventions
The intervention being considered is testing with a nucleic acid-based GIpathogen panel. These panels are capable of qualitatively detecting the DNA or RNA of multiple pathogens, including but not limited to *Campylobacter*, *Clostridioides (Clostridium) difficile*, *Plesiomonas shigelloides*, *Salmonella* spp., *Yersinia* spp., enteroaggregative *Escherichia coli*, enteropathogenic *E coli*, enterotoxigenic *E coli*, Shiga toxin-producing *E coli*, *E coli* O157, Shigella/enteroinvasive *E coli*, adenovirus F 40/41, astrovirus, norovirus, rotavirus, and sapovirus. For community-acquired diarrheal illness, extensive GI panels for parasites and viruses may be unnecessary because these illnesses are usually self-limited and, as viruses, are treated with supportive care and hydration.[10,] In situations in which the GI condition is likely foodborne based on patient history, GI pathogen panels may be limited to the most common pathogens typically found with foodborne illness. For patients who are immune competent, such a panel could include *Salmonella*, *Campylobacter*, *Shigella*, *Cryptosporidium* (parasite), Shiga toxin-producing *E. coli* (STEC), and STEC O157. More pathogen targets may be included if testing for *C. difficile* or testing patients who are critically ill or immunocompromised.[10,]

Patients with signs and/or symptoms of gastroenteritis and GI conditions are managed by primary care clinicians, infectious disease specialists, and emergency medicine professionals in an emergency or inpatient clinical setting. Time to a result of testing with a gastrointestinal pathogen panel is reduced compared with standard laboratory techniques (< 6 hours).[11,]

Comparators
Comparators of interest include no GI pathogen-specific testing and culture or nucleic acid-based testing for individual pathogens.

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, subsequent testing, and delay of correct diagnosis and treatment.[12,13,]

Though not completely standardized, follow-up for suspected gastroenteritis or GI conditions would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.

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Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Infectious gastroenteritis may be caused by a broad spectrum of pathogens resulting in the primary symptom of diarrhea. Panels for GI pathogens use multiplex amplified probe techniques and multiplex reverse transcription for the simultaneous detection of many GI pathogens such as *C. difficile*, *E. coli*, *Salmonella*, *Shigella*, norovirus, rotavirus, and *Giardia*. The performance study of the first FDA-cleared GI panel (xTAG Gastrointestinal Pathogen Panel [GPP], Luminex Molecular Diagnostics, Inc, Toronto, Ontario, CA), showed high sensitivity and specificity and overall strong positive percent agreement for the organisms on the panel (Table 7).[14]

Table 7. Prospective Performance Data by Organism

Organism	Sensitivity, %	95% CI, %	Specificity, %	95% CI, %
Campylobacter	100	43.8–100	98.2	97.3–98.8
Cryptosporidium	9.23	66.7–98.6	95.5	94.2–96.6
***E. coli* O157**	100	34.2–100	99.2	98.5–99.6
Giardia	100	51.0–100	96.7	95.5–97.6
Salmonella	100	72.2–100	98.4	97.6–99.0
STEC	100	20.7–100	98.6	97.8–99.2
Shigella	100	34.2–100	98.5	97.7–99.1
Organism	Positive Percent Agreement	95% CI, %	Negative Percent Agreement	
***C. difficile* Toxin A/B**	93.9	87.9–97.0	89.8	87.8–91.5
ETEC	25.0	7.1–59.1	99.7	99.1–99.9
Norovirus GI/GII	94.9	87.5–98.0	91.4	89.6–92.9
Rotavirus A	100	34.2–100	99.8	99.4–100

Source: FDA Decision Summary.[14]
CI: Confidence Interval; ETEC: enterotoxigenic *Escherichia coli;* GI: gastrointestinal; STEC: Shiga toxin–producing *E. coli.*

Several studies of GIpathogen panels have demonstrated overall high sensitivities and specificities and indicated the panels might be useful for detecting causative agents for GI infections, including both foodborne and infectious pathogens. Claas et al. (2013) assessed the performance characteristics of the xTAG Gastrointestinal Pathogen Panel (GPP; Luminex, Toronto, ON, Canada) compared with traditional diagnostic methods (ie, culture, microscopy, enzyme immunoassay/direct fluorescent antibody, real-time PCR (rtPCR), or sequencing) using

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901 stool samples from multiple sites[15]. The sensitivity of GPP against rtPCR was > 90% for nearly all pathogens tested by rtPCR; the 1 exception was adenovirus at 20%, but sensitivity could be higher because rtPCR did not distinguish between adenovirus species. Kahre et al. (2014) found similar results when they compared the FilmArray GI panel (BioFire Diagnostics, Salt Lake City, UT, USA) with the xTag GPP. Both panels detected more pathogens than routine testing. Of 230 prospectively collected samples, routine testing identified 1 or more GI pathogens in 19 (8.3%) samples; FilmArray detected 76 (33.0%), and xTag detected 69 (30.3%). Two of the most commonly detected pathogens in both assays were *C. difficile* (12.6%–13.9% prevalence) and norovirus (5.7%–13.9% prevalence). Both panels showed > 90% sensitivity for the majority of targets.

Using the xTAG GPP, Beckmann et al (2014) evaluated 296 patients who were either children with gastroenteritis (n = 120) or patients who had been to the tropics and had suspected parasite infestation (adults, n = 151; children, n = 25).[11] Compared with conventional diagnostics, the GPP showed 100% sensitivity for rotavirus, adenovirus, norovirus, *C. Salmonella difficile*, *species*, *Cryptosporidium*, and *Giardia lamblia*. Specificity was >90% for all but norovirus (42%) and *G. lamblia* (56%), which both also had lower positive predictive value (PPV) at 46% and 33%, respectively. Salmonella species also had low PPV at 43%; all others had 100% PPV. Negative predictive value was 100% for all pathogens.

Buchan et al. (2013) evaluated a multiplex rtPCR assay (ProGastro SSCS, Gen-Probe Prodesse, San Diego, CA) limited to *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. against culture; and they tested for Shiga toxin-producing Escherichia coli (STEC) against broth enrichment followed by enzyme immunoassay[16]. A total of 1244 specimens from 4 U.S. clinical laboratories were tested. Bidirectional sequencing was used to resolve discrepancies between ProGastro and culture or enzyme immunoassay. The overall prevalence of pathogens detected by culture was 5.6%, whereas the ProGastro assay and bidirectional sequencing showed an overall prevalence of 8.3%. The ProGastro SSCS assay showed a sensitivity of 100% and a specificity of 99.4% to 100% for all pathogens. This is compared with a sensitivity of 52.9% to 76.9% and a specificity of 99.9% to 100% for culture compared with ProGastro SSCS assay.

Al-Talib et al. (2014) assessed the diagnostic accuracy of a pentaplex PCR assay with specific primers to detect hemorrhagic bacteria from stool samples.[17] The primers, which were mixed in a single reaction tube, were designed to detect *Salmonella* spp., *Shigella* spp., enterohemorrhagic *E. coli* , and *Campylobacter* spp., all of which are a particular danger to children in developing countries. The investigators used 223 stool specimens from healthy children and spiked them with hemorrhagic bacteria. All primers designed had 100% sensitivity, specificity, PPV, and negative predictive value.

Jiang et al. (2014) developed a reverse transcription and multiplex rtPCR assay to identify 5 viruses in a single reaction.[18] The viruses included norovirus genogroups I and II; sapovirus genogroups I, I, IV, and V; human rotavirus A; adenovirus serotypes 40 and 41; and human astrovirus. Compared with monoplex rtPCR, multiplex rtPCR assay had sensitivity ranging from 75% to 100%; specificity ranged from 99% to 100%.

The health technology assessment and systematic review by Freeman et al (2017) evaluated multiplex texts to identify GI pathogens in people suspected of having infectious gastroenteritis.[19] Tests in the assessment were xTAG® GPP and FilmArray GI Panel. Eligible study included patients with acute diarrhea, compared multiplex GI pathogen panels tests with standard microbiology tests, and assessed patient, management, and/or test accuracy outcomes. Of the 23 identified studies, none provided an adequate reference standard for comparing the accuracy of GI panels with standard tests, so sensitivity and specificity analyses were not performed. Positive and negative test agreement were analyzed for individual pathogens for the separate panel products and are not detailed in this review. The meta-analysis of 10 studies found high heterogeneity in participants, country of origin, conventional methods used, and pathogens considered. Using conventional methods as the determinant of

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clinically important disease, the meta-analysis results suggested GI panel testing is reliable and could supplant current microbiological methods. An increase in false positives would result, along with the potential for overdiagnosis and incorrect treatment. However, if GI panel testing is identifying important pathology being missed with conventional methods, the result could be more appropriate treatments. The clinical importance of these findings is unclear, and assessment of GI panel testing effect on patient management and outcomes, compared with conventional testing, is needed.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCT.

No RCTs were available that evaluated clinical utility

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. A 9-month, prospective, multi-center study by Cybulski et al. (2018) assessed the effect of the BioFire FilmArray GI PCR panel on clinical diagnosis and decision-making. It also compared the diagnostic accuracy for patients with positive results obtained exclusively using the GI panel with results obtained using conventional stool culture.[20] (Study characteristics in Table 8.) Testing on 1887 consecutive fecal samples was performed in parallel using the GI panel and stool culture. The GI panel detected pathogens in significantly more samples than culture; median time from collection to results and collection to initiation of treatment was also significantly less. The use of a GI panel also led to a significant trend toward targeted therapy rather than empirical (r^2=0.65; *p*=0.009 by linear regression). Results of the GI panels resulted in discontinuation of antimicrobials in 8 of 9 Shiga toxin-producing *E. coli* (STEC), with just 1 example of GI panel results affecting clinical decision-making. (Other results summarized in Table 9.) Limitations of the study include the limit to 2 hospitals within a single healthcare system and certain subgroups that were too small for analysis. In addition, it was unclear how the historic controls were used since the current samples tested were both tested with GI panel and culture.

The prospective study by Beal et al. (2017) also aimed to assess the clinical impact of the BioFire FilmArry GI panel.[21] (Study characteristics in Table 8.) Stool samples from 241 patients (180 adults and 61 children) were tested with the GI panel and compared with 594 control patients from the previous year who were tested via culture. The most common pathogens detected by the GI panel were enteropathogenic *E. coli* (n=21), norovirus (n=21), rotavirus (n=15), sapovirus (n=9), and *Salmonella* (n=9). GI panel patients had significantly fewer subsequent infectious stool tests compared with the control group. GI panel patients also had 0.18 imaging studies per patient compared with 0.39 (*p*=.0002) in the control group. The GI panel group spent fewer days on antibiotic(s) per patient: 1.73 versus 2.12 in the control group. In addition, average length of time from stool culture collection to discharge was 3.4 days for the GI panel group and 3.9 days for the controls (*p*=.04). (Other results summarized in Table 9.) The GI panel improved patient care in several ways: (1) it identified a range of pathogens that might not have been detected by culture, (2) it reduced the need for other diagnostic tests, (3) it resulted in less unnecessary use of antibiotics, and (4) it led to shorter length of hospital stay. Some limitation of the study include not confirming the results in which the GI panel did not agree with standard testing, and the study used a historical cohort as a control group.

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Table 8. Summary of Key Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Test 1	Test 2
Cybulski (2018)[20]	Prospective multi-center, parallel design	U.S.	Jan-Sep 2017 (controls from 2016)	Newly admitted inpatients (<3 d) and outpatients aged 0-91 y; historical control group was patients with positive stool samples from same laboratory during the same period the previous year. (N=1887 specimens)	BioFire FilmArray GI panel (n=1887 specimens)	Stool culture (n=1887)
Beal (2017)[21]	Prospective single-center	U.S.	Jun 2016-Jun 2017 (controls from Jun-Dec 2015)	ED or admitted patients with stool samples submitted with an order for culture; historical controls were from a previous period.(N=835)	BioFire FilmArray GI Panel (n=241)	Stool culture (n=594)

ED: emergency department; GI: gastrointestinal.

Table 9. Summary of Key Observational Comparative Study Results

Study	Pathogens Detected, % of specimens	Time to Results	Time From Collection to Treatment	Empirical Initiation of Antimicrobial, %	Overall Positivity Rate, %	No. of Additional Stool Tests
Cybulski et al. (2018)[20]		Median	Median			
GI panel	35.3	18 h	26 h	23.5	NR	NR
Culture	6.0	47 h	72 h	40.0	NR	NR
***p*-value**	NA	<.0001	<.0001	.015	NR	NR
Beal et al (2017)[21]		Mean				
GI panel	NR	8.94 h	NR	NR	32.8	0.58
Culture	NR	54.75 h	NR	NR	6.7	3.02
95% CI	NA	1.44 to 82.8	NR	NR	NR	2.89 to 3.14
***p*-value**	NA	<.0001	NR	NR	NR	.0001

CI: confidence interval; GI: gastrointestinal; NA: not applicable; NR: not reported.

Section Summary: Gastrointestinal Pathogen Panel

Most GI panels combining multiple individual nucleic acid tests provide faster results compared standard stool culture. Sensitivity and specificity are generally high, but the yield of testing may be affected by the panel composition. Results of comparisons of conventional methods for ova and parasites to nucleic acid tests are limited. No direct evidence is available to assess clinical utility. Prospective observational studies were available to evaluate the clinical utility of a GI panel, which was shown in faster turnaround times leading to quicker treatment and a trend away from empirical treatment toward targeted therapy. However, both studies were limited by lack of adjudication of discordant results or the use of only a historical control. Access to a rapid method for etiologic diagnosis of GI infections may lead to more effective early treatment and infection-control measures. However, in most instances, when there is suspicion for a specific pathogen, individual tests could be ordered or a limited pathogen panel could be used. There may be a subset of patients with an unusual presentation who would warrant testing for a larger panel of pathogens at once, but that subset has not been well defined.

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Respiratory Pathogen Panel
Clinical Context and Test Purpose
The purpose of the nucleic acid-based respiratory pathogen panel is to provide a diagnostic option that is an alternative to or an improvement on existing tests in patients with signs and/or symptoms of viral or bacterial respiratory infections.

The question addressed in this evidence review is: Does testing for microorganisms using nucleic acid-based respiratory pathogen probes improve the health outcome in individuals with suspected viral or bacterial respiratory infections?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with signs and/or symptoms of viral or bacterial respiratory infections.
The available evidence also notes that respiratory pathogen panels are particularly effective for high-risk individuals.
High-risk individuals can include:
- Immunocompromised individuals, such as
    - Hematopoietic stem cell or solid organ transplant recipients
    - Individuals receiving high-dose chemotherapy and/or steroids
    - These individuals can be adult or pediatric patients
- Adults who appear acutely ill with respiratory conditions—particularly in certain settings such as influenza outbreaks
- Critically ill adult individuals—particularly ICU patients

Interventions
The test being considered is the nucleic acid-based respiratory pathogen panel. The respiratory pathogens panel is used to diagnosis respiratory infection due to bacteria or viruses and to help guide management of the infection. This panel is performed primarily when a patient is seriously ill, hospitalized, and/or at an increased risk for severe infection with complications or multiple infections. Not everyone with symptoms is tested (e. g., fever, aches, sore throat, and cough). Samples are collected by nasopharyngeal swab in universal transport medium or respiratory wash (i.e. , nasal wash, nasal aspirate, or bronchoalveolar lavage wash). Examples of these pathogens include adenovirus, coronavirus (HKU1, NL63, 229E, OC43), human metapneumovirus, human rhinovirus/enterovirus, influenza A (H1, H1-2009, H3), influenza B, parainfluenza (1, 2, 3, 4), respiratory syncytial virus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*. Patients are tested in an outpatient setting.

Comparators
Comparators of interest include no respiratory pathogen-specific testing and culture or nucleic acid-based testing for individual pathogens.

Outcomes
The general outcomes of interest are test accuracy, test validity, and other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, subsequent testing, and delay of correct diagnosis and treatment.

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Follow-up typically occurs in the days and weeks after diagnosis decision and initiation of treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Huang et al. (2018) published a systematic review and meta-analysis of a multiplex PCR system for the rapid diagnosis of respiratory virus infections.[22] Authors summarized diagnostic accuracy evidence on the detection of viral respiratory infections for BioFire FilmArray RP (Film Array), Nanosphere Verigene RV+ test, and Hologic Gen-Probe Prodesse assays. The study reviewed 20 studies with 5510 patient samples. Multiplex PCRs were found to have high diagnostic accuracy with AUROC $\geq$ 0.98 for all reviewed viruses expected adenovirus (AUROC 0.89). All 3 reviewed multiplex PCR systems were shown to be highly accurate.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Several studies of various respiratory viral panels have demonstrated the multiplex assay detected clinically important viral infections in a single genomic test and thus, may be useful for detecting causative agents for respiratory tract disorders.[23,24,25]

Randomized Controlled Trials

Andrews et al. (2017) published a quasi-randomized study assessing the impact of multiplex PCR on length of stay and turnaround time compared with routine, laboratory-based testing in the treatment of patients aged ≥ 16 years presenting with influenza-like illness or upper or lower respiratory tract infection.[26] (See Table 10 for study characteristics.) Patients were selected at inpatient and outpatient clinics in 3 areas of a hospital. FilmArray RP PCR systems were used. Of eligible patients (N=606), 545 (89.9%) were divided into a control arm (n=211) and an intervention arm (n=334). While PCR testing was not associated with a reduction in length of stay, turnaround time was reduced. (See Table 11 for detailed results.) Limitations of the study included design and patient allocation (patients were allocated to the intervention arm on

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even days). Additionally, the patients considered in the study were not noted to be high-risk individuals as defined above, only those with pertinent symptoms.

The parallel-group, open-label RCT by Brendish et al.(2017) evaluated the routine use of molecular point-of-care testing (POCT) for respiratory viruses in adults presenting to a hospital with acute respiratory illness [27]. (See Table 10 for study characteristics.) In a large U.K. hospital, over 2 winter seasons, investigators enrolled adults within 24 hours of presenting to the emergency department or acute medical unit with acute respiratory illness or fever > 37.5°C, or both. A total of 720 patients were randomized (1:1) to either molecular POCT for respiratory viruses (FilmArray Respiratory Panel; n = 362) or routine care (n = 358), which included diagnosis based on clinical judgment and testing by laboratory PCR at the clinical team's discretion. All patients in the POCT group were tested for respiratory viruses; 158 (45%) of 354 patients in the control group were tested. Because patients presenting with symptoms are often put on antibiotics before tests can be run, the results of the POCTs were unable to influence the outcome in many patients; therefore, a subgroup analysis was necessary for those who were only given antibiotics after test results were available. The results of the analysis showed antibiotics were prescribed for 61 (51%) of 120 patients in the POCT group and for 107 (64%) of 167 in the control group (difference = -13.2%; 95% CI, -24.8% to -1.7%; p =.0289). Mean test turnaround time for POCT was 2.3 hours (SD = 1.4) versus 37.1 hours (SD = 21.5) in the control group. The percentage of patients prescribed a neuraminidase inhibitor who tested positive for influenza was significantly higher for the POCT group than the control group (82% vs. 47%), and it was significantly lower for the percentage who tested negative for influenza (18% vs. 53%). In addition, the time to first dose was 8.8 hours (SD = 15.3) for POCT and 21.0 hours (SD = 28.7) for the control group. (See Table 11 for more results.) Blinding of the clinical teams to which group a patient had been randomized to was not possible because the purpose of the study was to inform the clinical team of POCT results. In addition, the limit of the study to the winter months means the findings cannot be extrapolated to the rest of the year.

Table 10. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Andrews et al. (2017)[a] [26]	United Kingdom	1	Jan-Jul 2015	Patients with influenza-like illness/upper RTI +/- lower RTI N = 454	FilmArray POC testing (even days of month) n = 334	Routine, laboratory-based RP PCR testing +/- atypical serology (odd days)n = 211
Brendish et al. (2017) [27]	United Kingdom	1	Jan 2015-Apr 2016 and Oct 2015-Apr, 2016[b]	Adults who could be recruited within 24 h of triage in ED or arrival at acute medical unit with acute respiratory illness or fever >37.5°C for ≤7 d N = 720	POCT n = 362	Diagnosis based on clinical judgment and PCR testing at clinical team's discretionn = 358

ARTI: acute respiratory tract infection; ED: emergency department; PCR: polymerase chain reaction; POCT: point of care testing (using FilmArray Respiratory Panel); RCT: randomized controlled trial; RP: respiratory panel; RTI: respiratory tract infection

[a] Quasi-randomized study

[b] The dates do not make sense because they overlap, likely due to an error in the article. Another place in the article says the "winter seasons in 2014-15 and 2015-16."

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Table 11. Summary of Key RCT Results

Study	Test Efficacy	Length of Stay	Antimicrobic Use Duration	All-Cause Mortality[a]	Readmission[b]
Andrews et al.(2017) [26]		Median (IQR)	Median (IQR)		
Active	24%	98.6 h (48.1–218.4)	6.0 d (4.0–7.0)	4%	19%
Comparator	20%	79.6 h (41.9–188.9)	6.8 d (5.0–7.3)	4%	20%
Estimated intervention effect	NR	NR	Absolute difference in natural logarithm of duration: -0.08 (95% CI: -0.22–0.054)	[a]OR: 0.9 (95% CI: 0.3–2.2)	OR: 0.9 (95% CI: 0.6–1.4)
Adjusted p-value	NR	NR	0.23	0.79	0.70
Brendish et al. (2017) [27]		Mean (SD)	Mean (SD)		
Active	NR	5.7 d (6.3)	7.2 d (5.1)	3%	13%
Comparator	NR	6.8 d (7.7)	7.7 d (4.9)	5%	16%
Difference (95% CI)	NR	-1.1 d (-2.2 to -0.3)	-0.4 (-1.2–0.4)[c]	-2.0% (-4.7%–0.6%)	-3.0% (-8.3%–2.0%)
OR (95% CI)	NR	NR	0.95 (0.85–1.05)[d]	0.54 (0.3–1.2)	0.78 (0.5–1.2)
p-value	NR	0.04	0.32	0.15	0.28

CI: confidence interval; IQR: interquartile range; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation.
[a] 30 days post-enrollment.
[b] Within 30 days of study participation.
[c] Mean risk difference.
[d] Unadjusted odds ratio.

The purpose of the limitations tables (Tables 12 and 13) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Andrews et al. (2017) [26]	2. Patients allocated to study arms based on even vs. odd days of the week; patient groups unbalanced in favor of FilmArray group					
Brendish et al. (2017)[27]		1. Patients and data collectors not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

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Table 13. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Andrews et al. (2017)[26]	4. Patients were not noted to be high-risk				
Brendish et al. (2017)[27]				3. Sensitivity and specificity not reported (study was on clinical utility)	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Respiratory Pathogen Panels

The evidence for the clinical validity or clinical utility of respiratory pathogen panels in diagnosing respiratory infections includes a systematic review and 2 RCTs. The systematic review reported that all 3 reviewed multiplex PCR systems were highly accurate. The clinical utility demonstrated by the RCTs showed benefits to the respiratory panel in test results turnaround time, time to receive treatment, and length of hospital stay. Significant differences were not seen in antibiotic prescription, readmission, or mortality.

Summary of Evidence

For individuals who have signs and/or symptoms of meningitis and/or encephalitis who receive a nucleic acid-based central nervous system pathogen panel, the evidence includes a systematic review and a pivotal prospective study. Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. Access to a rapid method that can simultaneously test for multiple pathogens may lead to the faster initiation of more effective treatment and conservation of cerebrospinal fluid. The available central nervous system panel is highly specific for the included organisms, but the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest clinical validity study were false-positives. A negative panel result does not exclude infection due to pathogens not included in the panel. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have signs and/or symptoms of gastroenteritis who receive nucleic acid-based gastrointestinal pathogen panel, the evidence includes prospective and retrospective evaluations of the tests' sensitivity and specificity and prospective studies on utility. Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. The evidence suggests that gastrointestinal pathogen panels are likely to identify both bacterial and viral pathogens with high sensitivity, compared with standard methods. Access to a rapid method for etiologic diagnosis of gastrointestinal infections may lead to more effective early treatment and infection-control measures. However, in most instances, when a specific pathogen is suspected, individual tests could be ordered. There may be a subset of patients with an unusual presentation who would warrant testing for a panel of pathogens at once, but that subset has not been well defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have signs and/or symptoms of respiratory infection who receive a nucleic acid-based respiratory pathogen panel, the evidence includes a systematic review and 2 randomized controlled trials (RCTs). Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. The systematic review reported that all 3 reviewed multiplex polymerase chain reaction systems were highly accurate. One RCT and 1 quasi-RCT evaluated utility of a respiratory panel and found benefits in time-to-treat and length of hospital stay; in addition, 1 subanalysis found fewer antibiotics being prescribed for patients diagnosed with the panel. The panel did not significantly affect duration of antibiotic use, readmission, or mortality rates. The evidence is sufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Numerous guidelines have been identified concerning the use of nucleic acid amplification tests (NAATs) for the diagnosis of the pathogens discussed in this review. Table 14 provides an index of NAAT recommendation by Virus/Infection.

Table 14. Index of NAAT Recommendations by Virus/Infection

Microorganism	Guidelines Recommending the Use of NAATs (Location)	Guidelines Not Recommending the Use of NAATs[a] (Location)
Bartonella hensalae	NIH (2.1.1), IDSA (3.1), AAP (5.1)	NA
Candida Species	CDC (1.5.1)[b]	IDSA (3.1, 3.7), AAP (5.1)
CNS Pathogen Panel	IDSA (3.2, 3.3)	NA
Chlamydia pneumonia	CDC (1.5.3), IDSA (3.1[c])	AAP (5.1)
Chlamydia trachomatis	CDC (1.5.2,[c] 1.6[c]), IDSA (3.1), AAP (5.1)	NA
Clostridium difficile	NIH (2.1.2), AAP (5.1)	IDSA (3.1, 3.4)
Cytomegolovirus	CDC (1.1), NIH (2.1.3), IDSA (3.1,[c] 3.3)	AAP (5.1)
Enterovirus	IDSA (3.1), AAP (5.1)	NA
Gardnerella vaginalis	AAP (5.1)	CDC (1.5.4), IDSA (3.1)
GI Pathogen Panel	CDC (1.4[c]), IDSA (3.5), ACG (6.1)	NA
Hepatitis B	NIH (2.1.4), IDSA (3.1), AAP (5.1)	NA
Hepatitis C	CDC (1.5.5[c]), NIH (2.1.5), IDSA (3.1), AAP (5.1)	NA
Herpes Simplex Virus	CDC (1.5.6[c]), NIH (2.1.6), IDSA (3.1,[c] 3.3), AAP (5.1)	NA
Human Herpesvirus 6	IDSA (3.1,[c] 3.3)	AAP (5.1)
Human Papillomavirus	CDC (1.5.8[c]), AAP (5.1)	NA
HIV 1	CDC (1.5.7[c]), IDSA (3.1), AAP (5.1)	NA
Influenza virus	IDSA (3.1[c]), AAP (5.1)	NA
Legionella pneumophila	IDSA (3.1), AAP (5.1)	NA
Meningitis	NA	IDSA (3.6)
Mycobacteria Species	CDC (1.8), NIH (2.1.7), IDSA (3.1, 3.3)	AAP (5.1)
Mycoplasma pneumoniae	CDC (1.2[c]), IDSA (3.3), AAP (5.1)	NA
Neisseria gonorrhoeae	CDC (1.6[c]), IDSA (3.1), AAP (5.1)	NA

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Microorganism	Guidelines Recommending the Use of NAATs (Location)	Guidelines Not Recommending the Use of NAATs[a] (Location)
Respiratory Panel	None Identified	NA
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	IDSA (3.8)	NA
Staphylococcus aureus	IDSA (3.1), AAP (5.1)	NA
Streptococcus, Group A	IDSA (3.1)	AAP (5.1)
Streptococcus, Group B	CDC (1.7), AAP (5.2)	IDSA (3.1), AAP (5.1)
Trichomonas vaginalis	CDC (1.5.9), IDSA (3.1),[c] AAP (5.1)	NA
Vancomycin-resistant enterococcus	AST (4.1)	IDSA (3.1), AAP (5.1)
Zika	CDC (1.3), IDSA (3.1), AAP (5.1)	NA

AAP: American Academy of Pediatrics; ACG: American College of Gastroenterology; AST: American Society of Transplantation; CDC: Centers for Disease Control and Prevention; IDSA: Infectious Disease Society of America; NA: not applicable (none found);
NAAT: nucleic acid amplification test; NIH: National Institutes of Health.
[a] Guidelines Not Recommending includes not only guidelines that recommend again NAATs but also those that were neutral on the use of NAATs.
[b] CDC recommends culture for first-line identification of *Candida* species; it recommends NAAT for complicated infections and for second-line diagnosis.
[c] Indicates guidelines in which the issuing body specifically recommends that U.S. Food and Drug Administration (FDA)-cleared NAATs be used.

A. Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) has published 10 recommendations and statements regarding the use of NAATs to diagnose the viruses and infections discussed in this evidence review since 2009.

In 2019, the CDC published guidance for laboratory testing for Cytomegolovirus (CMV), the guideline stated that the standard laboratory test for congenital CMV is polymerase chain reaction (PCR) on saliva, with confirmation via urine test to avoid false-positive results from ingesting breast milk from CMV seropositive mothers. Serologic tests were recommended for persons > 12 months of age.[28]

In 2018, the CDC published diagnostic methods for mycoplasma pneumoniae.[29] They cited NAAT as a method of diagnosis, along with culture or serology.

In 2017, the CDC published updated interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection.[30] It recommended:

- Asymptomatic pregnant women with ongoing possible Zika virus exposure (residing in or frequently traveling to an area with risk for Zika virus transmission) should be offered a Zika virus nucleic acid test (NAT) as part of routine obstetric care; and
- For infants with possible Zika virus infection, "if cerebrospinal fluid (CSF) is obtained for other purposes, NAT and IgM antibody testing should be performed on CSF because CSF was the only sample that tested positive in some infants with congenital Zika virus syndrome."

In 2017, the CDC updated its guidelines on norovirus gastroenteritis outbreak management and disease prevention.[31,32] Real-time reverse transcription-PCR assays, specifically, TaqMan-based real-time assays, which can contain multiple probes, is considered the effective laboratory diagnostic protocol for testing suspected cases of viral gastroenteritis.

In 2015, the following recommendations were made for the use of NAATs in diagnosing sexually transmitted diseases[33] For Candida Species:

- "PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis."
- For Chlamydia and Gonorrhea:

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- "NAATs for chlamydia and gonorrhea are recommended because of their high sensitivity and specificity; a specific diagnosis can potentially reduce complications, re-infection, and transmission."
- "Pregnant women found to have chlamydial infection should have a test-of-cure to document chlamydial eradication (preferably by nucleic acid amplification testing [NAAT]) 3–4 weeks after treatment and then retested within 3 months. Screening during the first trimester might prevent the adverse effects of chlamydia during pregnancy, but evidence for such screening is lacking."
- "NAAT performed on rectal specimens is the preferred approach to testing."
- For follow-up, "the use of chlamydial NAATs at <3 weeks after completion of therapy is not recommended because the continued presence of nonviable organisms can lead to false-positive results."

For Chlamydia pneumoniae:

- NAAT is recommended as an alternative to tissue culture, which "is the definitive standard diagnostic test for chlamydial pneumonia… NAATs are not FDA-cleared for the detection of chlamydia from nasopharyngeal specimens, and clinical laboratories must verify the procedure according to CLIA regulations."

For Gardnerella vaginalis:

- Although PCR has been researched "for the detection of various organisms associated with BV [bacterial vaginosis]," its clinical utility has not yet been established.

For Hepatitis C infection:

- NAATs are recommended for screening pregnant women with known risk factors; NAAT "is necessary to confirm the diagnosis of current HCV infection."
- In addition, "testing for HCV infection should include use of an FDA-cleared test for antibody to HCV…followed by NAAT to detect HCV RNA for those with a positive antibody result.

For Herpes Simplex Virus:

- "Cell culture and PCR are the preferred HSV tests for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions;" and
- "PCR is the test of choice for diagnosing HSV infections affecting the central nervous system and systemic infections."

For HIV-1:

- The use of NAAT is not mentioned; serologic tests are recommended for detecting antibodies against HIV-1 and by virologic tests that detect HIV antigens or RNA.

For Human Papillomavirus:

- There are several FDA-cleared HPV tests that detect viral nucleic acid or messenger RNA; however, there are currently no algorithms for HPV 16/18/45 testing in the clinical guidelines;
- The "use of non-oncogenic tests is not recommended;" and
- "HPV assays should be FDA-cleared and used only for the appropriate indications" and should not be performed if the patient is "deciding whether to vaccinate against HPV;" while "conducting STD screening in women or men at risk for STDs;" when "providing care to persons with genital warts or their partners;" when "conducting screening for cervical cancer as a stand-alone test;" when "testing women aged <30 years as part of routine cervical cancer screening;" or when "testing oral or anal specimens."

For Trichomonas vaginalis:

- NAAT is recommended for detecting *vaginalis* in women due to its high sensitivity and specificity. The APTIMA *T. vaginalis* assay (Hologic Gen-Probe, San Diego, CA) is FDA-cleared to detect *T. vaginalis* from vaginal, endocervical, or urine specimens for women.

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- In 1 study, "[f]or *vaginalis* diagnosis in men, the sensitivity of self-collected penile-meatal swabs was higher than that of urine." However, there is currently no FDA-cleared test for men.

In 2014, the CDC published recommendations regarding the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae infections. It stated:

- NAATs are superior other available diagnostic tests in "overall sensitivity, specificity, and ease of specimen transport;"
- The use of "NAAT to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls" is supported by evidence; and
- Only NAATs that have been cleared by the FDA for detection of C. trachomatis and N. gonorrhoeae "as screening or diagnostic tests because they have been evaluated in patients with and without symptoms" should be used.

In 2010, the CDC published guidelines on perinatal group B streptococcus (GBS) disease. [34] It stated:

- The use of NAATs with the addition of an enrichment broth to the sample increases NAAT sensitivity for GBS to 92.5%-100.0%;
- However, "data on the currently available assays do not support their use in replacement of antenatal culture or risk-based assessment of women with unknown GBS status on admission for labor;" and
- Because of the additional time needed to enrich samples, NAAT with enrichment is "not feasible for intrapartum testing, and the sensitivity of assays in the absence of enrichment is not adequate in comparison to culture."

In 2009, the CDC published updated guidelines for the use of NAATs in diagnosing Mycobacterium tuberculosis bacteria. The CDC recommended that "NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities." Although it noted that "culture remains the gold standard for laboratory confirmation of TB and is required for isolating bacteria for drug-susceptibility testing and genotyping," the guideline stated that "NAA testing should become standard practice for patients suspected to have TB, and all clinicians and public health TB programs should have access to NAA testing for TB to shorten the time needed to diagnose TB from 1–2 weeks to 1–2 days."

National Institute of Health et al

In 2019, the NIH, CDC, and HIV Medicine Association of the IDSA published guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV.[35] NAATs are discussed in the following situations:

Bartonella species

- For patients with suspected bacillary angiomatosis, serologic tests are the standard of care for diagnosing Bartonella infection. There are PCR "methods that have been developed for identification and speciation of Bartonella but are not widely available."

Clostridium difficile

- Routine testing with PCR is necessary for patients with diarrhea who have "recently received or are currently receiving antibiotics or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 week, those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medication, and those with moderate-to-severe community-acquired diarrhea."

Cytomegalovirus

- For patients with suspected cytomegalovirus disease, "viremia can be deterred by PCR" and "a positive result is highly suggestive that CMV is the cause of end-organ disease. However, PCR assays are not standardized; therefore, sensitivity, specificity, and interassay comparability are not clearly delineated."

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Hepatitis B
- The CDC, the United States Preventive Services Task Force, and the AASLD recommend that patients with HIV infection should be tested for hepatitis B; however, NAATs are not recommended for initial testing in patients with HIV.

Hepatitis C
- Patients with HIV are recommended to undergo routine hepatitis C screening, initially "performed using the most sensitive immunoassays licensed for detection of antibody to HCV in blood." The use of NAATs are not mentioned for initial testing in patients with HIV.

Herpes Simplex Virus
- "HSV DNA PCR… is the preferred method for diagnosis of mucocutaneous HSV lesions caused by HSV."

Mycobacterium tuberculosis Infection and Disease
- "It is recommended that for all patients with suspected pulmonary TB, an NAA test be performed on at least one specimen."
  - "Rapid diagnosis is essential in patients with HIV given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB."
  - "NAA tests have at least two uses among patients with suspected HIV-related TB. First, NAA assays, if positive, are highly predictive of TB disease when performed on AFB smear-positive specimens…. Second, NAA tests are more sensitive than AFB smear, being positive in 50% to 80% of smear-negative, culture-positive specimens and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen."

Infectious Disease Society of America et al
Since 2008, the IDSA has partnered with various societies to publish 9 recommendations regarding the use of NAATs to diagnose the viruses and infections discussed in this evidence review.

In 2018, the IDSA and the American Society for Microbiology published a guide on the diagnosis of infectious diseases[36]. NAATs were recommended diagnostic procedures for Enterovirus, Hepatitis C, Hepatitis B, Cytomegalovirus, Herpes Simplex Virus, Human Herpesvirus 6, HIV, Influenza Virus, and Zika Virus. NAATs were not recommended diagnostic procedures for Bacterial vaginosis. In addition to providing guidance on diagnosing these diseases, the guidelines also provided recommendations on testing for other conditions by testing for common etiologic agents. Table 15 describes the conditions for which IDSA recommends NAATs for diagnosing etiologic agents.

Table 15. IDSA Recommended Conditions for Use of NAATs in Identifying Etiologic Agents of Other Conditions*

Etiologic Agents	Recommended Conditions for Use of NAATs in Diagnosis when Specific Etiologic Agents is Suspected
Bartonella spp	Bloodstream infections
Chlamydia pneumoniae	Bronchiolitis, Bronchitis, and Pertussis; Community-Acquired Pneumonia
Chlamydia trachomatis	Periocular structure infections/ Conjunctivitis, Orbital and Periorbital Cellulitis, and Lacrimal and Eyelid Infections; Proctitis; Epididymitis and Orchitis; Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis
Clostridium difficile	Gastroenteritis, Infectious, and Toxin-Induced Diarrhea
Cytomegalovirus	Pericarditis and Myocarditis[a]; Encephalitis; Pneumonia in the Immunocompromised Host; Esophagitis; Gastroenteritis, Infectious, and Toxin-Induced Diarrhea; Burn Wound Infections[b]
Enterovirus	Meningitis; Encephalitis; Brochiolitis, Bronchitis, and Pertussis; Community-Acquired Pneumonia; Gastroenteritis, Infectious, and Toxin-Induced Diarrhea
Herpes Simplex Virus	Meningitis; Encephalitis; Immunocompromised Host; Esophagitis; Proctitis; Pathogens Associated with Cervicitis/Urethritis; Burn Wound Infection[b]; Periocular structure infections/ Conjunctivitis, Orbital and

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Etiologic Agents	Recommended Conditions for Use of NAATs in Diagnosis when Specific Etiologic Agents is Suspected
	Periorbital Cellulitis, and Lacrimal and Eyelid Infections; Periocular Structure Infections/Keratitis; Pharyngitis; Genital Lesions
HIV	Pericarditis and Myocarditis; Meningitis[c]; Pharyngitis[c]
Human Herpesvirus 6	Encephalitis
Influenza	Encephalitis; Bronchiolitis, Bronchitis, and Pertussis; Community-Acquired Pneumonia; Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia; Pulmonary Infections in Cystic Fibrosis;
Legionella spp	Community-Acquired Pneumonia; Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia; Infections of the Pleural Space; Surgical Site Infections
Mycobacteria Species- both Tuberculosis and NTM	Community-Acquired Pneumonia; Infections of the Pleural Space; Osteomyelitis
Neisseria gonorrhoeae	Pharyngitis; Proctitis; Native Joint Infection and Bursitis; Epididymitis and Orchitis; Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis
Staphylococcus aureus	Burn Wound Infections for MRSA and S. aureus only, Trauma-Associated Cutaneous Infections; Surgical Site Infections
Streptococcus, Group A	Pharyngitis
Trichomonas vaginalis	Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis

* The IDSA provided recommendations for many situations in which NAATs are recommended for diagnosing certain etiologic agents commonly seen with the listed conditions noted under the Recommended Conditions for Use of NAATs in Diagnosis Column.
HIV: human immunodeficiency virus; IDSA: Infectious Disease Society of America; MSRA: methicillin-resistant Staphylococcus aureus; NAAT: nucleic acid amplification test: NTM: nontuberculous mycobacteria.
[a] Recommended as first choice if available;
[b] Where applicable and laboratory-validated;
[c] The guidelines caution that NAAT is not 100% sensitive in individuals with established HIV infection due to viral suppression; therefore, if NAAT is used, subsequent serologic testing is recommended.

NAATs for diagnosing *Candida* species, *Gardnerella vaginalis*, *Streptococcus* Group B, and Vancomycin-resistant enterococcus as etiologic agents were not recommended.

In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis.[37] When making diagnostic recommendations, the IDSA notes cultures as the standard of care in diagnosing healthcare-associated ventriculitis and meningitis, but that "nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low)." (Strength of recommendation and quality of evidence established using the GRADE [Grading of Recommendations Assessment, Development and Evaluation] methodology.[37])

In 2008, the IDSA published clinical practice guidelines for the management of encephalitis.[38] The following recommendations were made:

- "Biopsy of specific tissues for culture, antigen detection, nucleic acid amplification tests (such as PCR), and histopathologic examination should be performed in an attempt to establish an etiologic diagnosis of encephalitis (A-III)." (Strength of recommendation level "A indicates good evidence to support recommendation for use." Quality of evidence level III indicates "evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees."[39])
- "Nucleic acid amplification tests (such as PCR) of body fluids outside of the CNS may be helpful in establishing the etiology in some patients with encephalitis (B-III)." (Strength of recommendation level B indicates "moderate evidence to support recommendation." Quality of evidence level III indicates "evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees."[39])
- "Nucleic acid amplification tests (such as PCR) should be performed on CSF specimens to identify certain etiologic agents in patients with encephalitis (A-III). Although a positive

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test result is helpful in diagnosing infection caused by a specific pathogen, a negative result cannot be used as definitive evidence against the diagnosis."
- The use of NAATs was recommended for diagnosing CMV, HSV-1 and -2, Human herpesvirus 6, Bartonella henselae, Mycoplasma pneumoniae, and Mycobacterium tuberculosis.

In 2018, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published weak recommendations with low quality evidence for the use of NAATs to diagnose Clostridium difficile.[40]
- "The best-performing method (i.e., in use positive and negative predictive value) for detecting patients at increased risk for clinically significant C. difficile [CDI] infection" is use of a "stool toxin test as part of a multistep algorithm…rather than NAAT along for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission."
- "The most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms" is use of "a NAAT alone or a multistep algorithm for testing…rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission."

In 2017, the IDSA published clinical practice guidelines for the diagnosis and management of infectious diarrhea.[41] The following recommendations were made:
- In situations where enteric fever or bacteremia is suspected, "culture-independent, including panel-based multiplex molecular diagnostics from stool and blood specimens, and when indicated, culture-dependent diagnostic testing should be performed" (GRADE: strong, moderate).
- In testing for Clostridium difficile in patients >2 years of age, "a single diarrheal stool specimen is recommended for detection of toxin or toxigenic C. difficile strain (e.g., nucleic acid amplification testing)" (GRADE: strong, low).
- NAATs are not recommended for diagnosing Cytomegalovirus.
- It was also noted that "clinical consideration should be included in the interpretation of results of multiple-pathogen nucleic acid amplification tests because these assays detect DNA and not necessarily viable organisms" (GRADE: strong, low).

In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis.[37] When making diagnostic recommendations, the IDSA notes cultures as the standard of care in diagnosing healthcare-associated ventriculitis and meningitis, but that "nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low)."

In 2016, the IDSA published updated clinical practice guidelines for managing candidiasis.[42] The guideline noted many limitations of PCR testing. No formal recommendation was made, but the guidelines did state that "the role of PCR in testing samples other than blood is not established."

In 2020, the IDSA established a panel composed of 8 members including frontline clinicians, infectious diseases specialists and clinical microbiologists who were members of the IDSA, American Society for Microbiology (ASM), Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). Panel members represented the disciplines of adult and pediatric infectious diseases, medical microbiology, as well as nephrology and gastroenterology. The panel created a COVID-19 Diagnosis guideline using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evidence assessment; and, given the need for rapid response to an urgent public health crisis, the methodological approach was modified according to the GIN/McMaster checklist for development of rapid recommendations. The panel published recommendations for COVID-19 Diagnosis in an online format, as when substantive new information becomes available the

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recommendations will require frequent updating.[43] The current recommendations (published May 6, 2020) support SARS-CoV-2 nucleic acid testing for the following groups:

- all symptomatic individuals suspected of having COVID-19;
- asymptomatic individuals with known or suspected contact with a COVID-19 case;
- asymptomatic individuals without known exposure when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy.

The IDSA panel further recommends the following:

- collecting nasopharyngeal, or mid-turbinate or nasal swabs rather than oropharyngeal swabs or saliva alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, very low certainty of evidence).
- nasal and mid-turbinate (MT) swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection (URTI) or influenza like illness (ILI) suspected of having COVID-19 (conditional recommendation, low certainty of evidence).
- a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample (conditional recommendations, very low certainty of evidence)
- performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).
- repeating viral RNA testing when the initial test is negative (*versus* performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).

The IDSA panel makes no recommendations for or against using rapid (i.e., test time ≤ 1hour) versus standard RNA testing in symptomatic individuals suspected of having COVID-19 (knowledge gap).

American Society of Transplantation

In 2019, the American Society of Transplantation Infectious Diseases Community of Practice published guidelines which addressed vancomycin-resistant enterococci infections in solid organ transplant patients.[44] The guidelines noted the cost-effectiveness and accuracy of "emerging molecular diagnostics for VRE colonization, including multiplexed PCR performed after culture on selective media," compared with culture alone.

American Academy of Pediatrics

The current edition of the AAP Red Book describes the diagnostic and treatment options of many infectious diseases in the pediatric population.[45] Their recommendations for appropriate diagnostic tests for the viruses and infections discussed in this policy are detailed in Table 16.

Table 16. Redbook Diagnostic Test Recommendations for the Pediatric Population

Infection	Diagnostic Test Recommendation
Bartonella henselae	IFA NAAT (PCR)
Candida Species	Clinical Evaluation Microscopy
Chlamydia pneumoniae	Serologic antigen test PCRs- "can provide a specific diagnosis but are not available in most clinical laboratories"
Chlamydia trachomatis	NAATs are recommended for C trachomatis urogenitial infections and in postpubescent individuals. They are not recommended for

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Infection	Diagnostic Test Recommendation
	diagnosis C trachomatis conjunctivitis or pneumonia or in the evaluation of prepubescent children for possible sexual assault.
Clostridium difficile	Anaerobic cultures of wound exudate and blood should be performed.
Cytomegalovirus	Saliva PCR is the preferred diagnostic tool for screening.
Enterovirus	Reverse-transcriptase PCR and culture from a variety of specimens
Gardnerella vaginalis	Microscopy Numerous NAATs have been recommended when microscopy is unavailable
Hepatitis B	Serologic antigen tests NAATs
Hepatitis C	IgG antibody enzyme immunoassays NAATs
Herpes Simplex Virus	Cell culture NAATs- diagnostic method of choice for neonates with CNS infections, older children, and adults with HSE
Human Herpesvirus 6	Few developed assays are available commercially and do not differentiate between new, past, and reactivated infection. Therefore, these tests "have limited utility in clinical practice:" Serologic tests; PCR- the assays are not sensitive in younger children.
HIV 1	HIV DNA PCR- "preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18mo; HIV RNA PCR- "preferred test to identify non-B subtype HIV-1 infections… DNA PCR is generally preferred because of greater clinical experience with that assay."
Human Papillomavirus	"Detection of HPV infection is based on detection of viral nucleic acid or capsid protein."
Influenza Virus	"RT-PCR, viral culture tests, and rapid influenza molecular assays offer potential for high sensitivity as well as specificity and are recommended as the tests of choice."
Legionella pneumophila	BCYE Media Legionella antigen in urine Direct IFA Genus-specific PCR reaction-based assays
Meningitis	Cultures of blood and CSF NAATs- "useful in patients who receive antimicrobial therapy before cultures are obtained."
Mycobacteria Species	M tuberculosis disease: Chest radiography and physical examination While several NAATs are cleared by the FDA, "further research is needed before NAATs can be recommended routinely for the diagnosis of tuberculosis in children," Nontuberculous Mycobacteria: "definite diagnosis of NTM disease requires isolation of the organism."
Mycoplasma pneumonia	"PCR tests for M pneumoniae are available commercially and increasing replacing other tests, because PCR tests performed on respiratory tract specimens have sensitivity and specifically between 80% and 100%, yield positive results earlier in the course of illness than serologic tests, and are rapid."
Neisseria gonorrhoeae	"NAATs are far superior in overall performance compared with other N gonorrhoeae culture and nonculture diagnostic methods to test genital and nongenital specimens, but performance varies by NAAT type."
Staphylococcus aureus	"NAATS are approved for detection and identification of S aureus, including MRSA, in positive blood cultures."
Streptococcus, Group A	"Children with pharyngitis and obvious viral symptoms should not be tested or treated for GAS infection. Laboratory confirmation is required for cases in children without viral symptoms… culture on sheep blood agar can confirm GAS infection."

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Infection	Diagnostic Test Recommendation
Streptococcus, Group B	"Gram-positive cocci in pairs or short chains by gram stain of body fluids that typically are sterile provide presumptive evidence of infection."
Trichomonas vaginalis	Microscopy NAATs are "the most sensitive mean of diagnosing T vaginalis infection and is encouraged for detection in females and males."
Vancomycin-resistant enterococcus	"Diagnosis is established by culture of usually sterile body fluids with appropriate biochemical testing and serologic analysis for definitive identification."
Zika	NAATs Trioplex real-time PCR assay Serologic testing

BCYE: buffered charcoal yeast extract; CNS: central nervous sytem; CSF: cerebrospinal fluid; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; HPV: human papillomavirus; HSE: herpes simplex encephalitis;
IFA: indirect fluorescent antibody; MSRA: methicillin-resistant Staphylococcus aureus; NAAT: nucleic acid amplification test; NTM: nontuberculous mycobacteria; PCR: polymerase chain reaction.

In 2019, the AAP published guidelines on managing infants at risk for GBS.[46] It recommends antenatal vaginal-rectal culture performed by using a broth enrichment "followed by GBS identification by using traditional microbiologic methods or by NAAT-based methods." However, point-of-care NAAT-based screening should not be the primary method of determining maternal colonization status due to reported variable sensitivity as compared with traditional culture, as well as "because most NAAT-based testing cannot be used to determine the antibiotic susceptibility of colonizing GBS isolates among women with a penicillin allergy."

American College of Gastroenterology

In 2016, the American College of Gastroenterology published clinical guidelines on the diagnosis, treatment, and prevention of acute diarrheal infections in adults.[47] It recommended that, given 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,… the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. (Strong recommendation, low level of evidence)." These are described in the rationale as multiplex molecular testing.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
During the Public Health Emergency for the COVID-19 pandemic, a number of Medicare exceptions and waivers have been implemented. For further information on testing, see the CMS website regarding Coronavirus Disease.[48]

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03809117	A Randomized Controlled Trial of Biofire Film Array Gastrointestinal Panel Compared to Usual Care for Evaluation of Acute Infectious Diarrhea in the Emergency Department	176	Nov 2019

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03551340	Impact of the Introduction of Gasto-intestinal Panel by PCR on the Treatment of Patients with Gastroenteritis	210	Mar 2020
NCT03895281	Clinical Evaluation of the FilmArray® Meningitis/Encephalitis (ME) Panel	150	Apr 2020
NCT03452826	Combined Use of a Respiratory Broad Panel MULTIplex PCR and Procalcitonin to Reduce Antibiotics Exposure in Patients With Severe Community-Acquired Pneumonia: a Multicentre, Parallel-group, Open-label, Randomized Controlled Trial (MULTI-CAP)	450	Aug 2020
NCT03362970	Improvements Through the Use of a Rapid Multiplex PCR Enteric Pathogen Detection Kit in Children With Hematochezia	60	Dec 2020
NCT03840603	PROARRAY: Impact on PCT+ FilmArray RP2 Plus Use in LRTI Suspicion in Emergency Department	444	Jan 2021
NCT04372004	Comparison of the Efficacy of Rapid Tests to Identify COVID-19 Infection (CATCh COVID-19) (CATCH COVID-19)	100	June 2021

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Microorganism in question
  - Past and present testing
  - Specific test being requested
- Laboratory results

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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 ***(Code revision effective 7/1/2020)***
	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
	0096U	Human Papillomavirus (HPV), high-risk types (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), male urine
	0097U	Gastrointestinal pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 22 targets (Campylobacter (C. jejuni/C. coli/C. upsaliensis), Clostridium difficile (C. difficile) toxin A/B, Plesiomonas shigelloides, Salmonella, Vibrio (V. parahaemolyticus/V. vulnificus/ V. cholerae), including specific identification of Vibrio cholerae, Yersinia enterocolitica, Enteroaggregative Escherichia coli (EAEC), Enteropathogenic Escherichia coli (EPEC), Enterotoxigenic Escherichia coli (ETEC) lt/st, Shiga-like toxin-producing Escherichia coli (STEC) stx1/stx2 (including specific identification of the E. coli O157 serogroup within STEC), Shigella/ Enteroinvasive Escherichia coli (EIEC), Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia (also known as G. intestinalis and G. duodenalis), Adenovirus F 40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, Sapovirus (Genogroups I, II, IV, and V))

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Type	Code	Description
	0098U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 14 targets (Adenovirus, Coronavirus, Human Metapneumovirus, Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype H1-2009, Influenza B, Parainfluenza Virus, Human Rhinovirus/Enterovirus, Respiratory Syncytial Virus, Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae) ***(Deleted code effective 4/1/2021)***
	0099U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 20 targets (Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus, Coronavirus OC43, Human Metapneumovirus, Influenza A, Influenza A subtype, Influenza A subtype H3, Influenza A subtype H1-2009, Influenza, Parainfluenza Virus, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Human Rhinovirus/Enterovirus, Respiratory Syncytial Virus, Bordetella pertussis, Chlamydophila pneumonia, Mycoplasma pneumoniae) ***(Deleted code effective 4/1/2021)***
	0100U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 21 targets (Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, including subtypes H1, H1-2009, and H3, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial Virus, Bordetella parapertussis (IS1001), Bordetella pertussis (ptxP), Chlamydia pneumoniae, Mycoplasma pneumoniae) ***(Deleted code effective 4/1/2021)***
	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
	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
	0151U	Infectious disease (bacterial or viral respiratory tract infection), pathogen specific nucleic acid (DNA or RNA), 33 targets, real-time semi-quantitative PCR, bronchoalveolar lavage, sputum, or

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Type	Code	Description
		endotracheal aspirate, detection of 33 organismal and antibiotic resistance genes with limited semi-quantitative results
	0500T	Infectious agent detection by nucleic acid (DNA or RNA), human papillomavirus (HPV) for five or more separately reported high-risk HPV types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) (i.e., genotyping)
	81513	Infectious disease, bacterial vaginosis, quantitative real-time amplification of RNA markers for Atopobium vaginae, Gardnerella vaginalis, and Lactobacillus species, utilizing vaginal-fluid specimens, algorithm reported as a positive or negative result for bacterial vaginosis ***(Code effective 1/1/2021)***
	81514	Infectious disease, bacterial vaginosis and vaginitis, quant real-time amp of DNA markers for Gardnerella vaginalis, Atopobium vaginae, Megasphaera type 1, Bacterial Vaginosis Assoc Bacteria-2 (BVAB-2), and Lactobacillus species ***(Code effective 1/1/2021)***
	81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (e.g., positive or negative for high probability of usual interstitial pneumonia [UIP]) ***(Code effective 1/1/2021)***
	87471	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, amplified probe technique
	87472	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, quantification
	87480	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique
	87481	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique
	87482	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, quantification
	87483	Infectious agent detection by nucleic acid (DNA or RNA); central nervous system pathogen (e.g., 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
	87485	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, direct probe technique
	87486	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, amplified probe technique
	87487	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, quantification
	87490	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique
	87491	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
	87492	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, quantification
	87493	Infectious agent detection by nucleic acid (DNA or RNA); Clostridium difficile, toxin gene(s), amplified probe technique
	87495	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, direct probe technique

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Type	Code	Description
	87496	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique
	87497	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, quantification
	87498	Infectious agent detection by nucleic acid (DNA or RNA); enterovirus, amplified probe technique, includes reverse transcription when performed
	87500	Infectious agent detection by nucleic acid (DNA or RNA); vancomycin resistance (e.g., enterococcus species van A, van B), amplified probe technique
	87501	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, includes reverse transcription, when performed, and amplified probe technique, each type or subtype
	87502	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, first 2 types or sub-types
	87503	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, each additional influenza virus type or sub-type beyond 2 (List separately in addition to code for primary procedure)
	87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets
	87506	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., 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 (e.g., 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
	87510	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, direct probe technique
	87511	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, amplified probe technique
	87512	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification
	87516	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, amplified probe technique
	87517	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, quantification
	87520	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique
	87521	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, amplified probe technique, includes reverse transcription when performed
	87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, quantification, includes reverse transcription when performed

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Type	Code	Description
	87525	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, direct probe technique
	87526	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, amplified probe technique
	87527	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, quantification
	87528	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, direct probe technique
	87529	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, amplified probe technique
	87530	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, quantification
	87531	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, direct probe technique
	87532	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, amplified probe technique
	87533	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, quantification
	87534	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, direct probe technique
	87535	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, amplified probe technique, includes reverse transcription when performed
	87536	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed
	87537	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, direct probe technique
	87538	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, amplified probe technique, includes reverse transcription when performed
	87539	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, quantification, includes reverse transcription when performed
	87540	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, direct probe technique
	87541	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, amplified probe technique
	87542	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, quantification
	87550	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, direct probe technique
	87551	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, amplified probe technique
	87552	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, quantification
	87555	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, direct probe technique
	87556	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, amplified probe technique
	87557	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, quantification
	87560	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, direct probe technique
	87561	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, amplified probe technique

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Type	Code	Description
	87562	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, quantification
	87563	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma genitalium, amplified probe technique
	87580	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, direct probe technique
	87581	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, amplified probe technique
	87582	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, quantification
	87590	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, direct probe technique
	87591	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
	87592	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, quantification
	87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (e.g., 6, 11, 42, 43, 44)
	87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
	87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
	87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets
	87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., 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 (e.g., 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
	87634	Infectious agent detection by nucleic acid (DNA or RNA); respiratory syncytial virus, amplified probe technique
	87640	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, amplified probe technique
	87641	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, methicillin resistant, amplified probe technique
	87650	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, direct probe technique
	87651	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, amplified probe technique
	87652	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, quantification
	87653	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group B, amplified probe technique

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Type	Code	Description
	87660	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique
	87661	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique
	87662	Infectious agent detection by nucleic acid (DNA or RNA); Zika virus, amplified probe technique
	87797	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
	87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
	87799	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/14/2013	BCBSA Medical Policy adoption
01/30/2015	Coding update
06/30/2015	Coding update
03/01/2016	Policy title change from Identification of Microorganisms: Nucleic Acid Probes and PCR Amplification. Policy revision with position change.
05/01/2016	Policy revision without position change
06/01/2017	Policy revision without position change
01/01/2018	Coding Update
02/01/2018	Policy revision without position change
10/01/2018	Coding Update
02/01/2019	Policy revision without position change
07/01/2019	Coding update
11/01/2019	Coding update
03/01/2020	Coding update
04/01/2020	Annual review. No change to policy statement.
08/01/2020	Policy statement, guidelines and literature updated. Coding update.
01/01/2021	Coding update.
06/01/2021	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Identification of Microorganisms Using Nucleic Acid Probes 2.04.10 **Policy Statement:** The use of nucleic acid testing using a direct or amplified probe technique (*without* quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms (see Policy Guidelines): • Bartonella henselae or quintana • Bordetella pertussis • Candida species • Chlamydia pneumoniae • Chlamydia trachomatis • Clostridium difficile • Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB) • Enterovirus • Herpes simplex virus • Human papillomavirus (HPV) • Influenza virus • Legionella pneumophila • Mumps • Mycobacterium species • Mycobacterium tuberculosis • Mycobacterium avium-intracellulare • Mycoplasma pneumoniae • Neisseria gonorrhoeae • Rubeola (measles) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) • Staphylococcus aureus • Staphylococcus aureus, methicillin-resistant • Streptococcus, group A • Streptococcus, group B • Trichomonas vaginalis • Zika virus	**Identification of Microorganisms Using Nucleic Acid Probes 2.04.10** **Policy Statement:** The use of nucleic acid testing using a direct or amplified probe technique (*without* quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms (see Policy Guidelines): I. Bartonella henselae or quintana II. Bordetella pertussis III. Candida species IV. Chlamydia pneumoniae V. Chlamydia trachomatis VI. Clostridium difficile VII. Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB) VIII. Enterovirus IX. Herpes simplex virus X. Human papillomavirus (HPV) XI. Influenza virus XII. Legionella pneumophila XIII. Mumps XIV. Mycobacterium species XV. Mycobacterium tuberculosis XVI. Mycobacterium avium-intracellulare XVII. Mycoplasma pneumoniae XVIII. Neisseria gonorrhoeae XIX. Rubeola (measles) XX. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) XXI. Staphylococcus aureus XXII. Staphylococcus aureus, methicillin-resistant XXIII. Streptococcus, group A XXIV. Streptococcus, group B XXV. Trichomonas vaginalis XXVI. Zika virus

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<table>
<tr><th colspan="2">POLICY STATEMENT
(No changes)</th></tr>
<tr><th>BEFORE</th><th>AFTER</th></tr>
<tr><td>The use of nucleic acid testing using a direct or amplified probe technique (with or without quantification of viral load) may be considered medically necessary for any of the following microorganisms:
• Cytomegalovirus
• Hepatitis B virus
• Hepatitis C virus
• Human herpesvirus 6
• Human Immunodeficiency Virus 1 (HIV-1)
• Human Immunodeficiency Virus 2 (HIV-2)

The use of nucleic acid testing with quantification of viral load is considered investigational for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered medically necessary.

The use of nucleic acid testing using a direct or amplified probe technique is considered investigational for the following microorganisms:
• Gardnernella vaginalis
• Hepatitis G

The use of the following nucleic acid testing panel (without quantification of viral load) may be considered medically necessary:
• Respiratory Virus Panel

The use of the following nucleic acid testing panels (with or without quantification of viral load for viral panel elements) is considered investigational:
• Central nervous system pathogen panel
• Gastrointestinal pathogen panel</td><td>The use of nucleic acid testing using a direct or amplified probe technique (with or without quantification of viral load) may be considered medically necessary for any of the following microorganisms:
I. Cytomegalovirus
II. Hepatitis B virus
III. Hepatitis C virus
IV. Human herpesvirus 6
V. Human Immunodeficiency Virus 1 (HIV-1)
VI. Human Immunodeficiency Virus 2 (HIV-2)

The use of nucleic acid testing with quantification of viral load is considered investigational for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered medically necessary.

The use of nucleic acid testing using a direct or amplified probe technique is considered investigational for the following microorganisms:
I. Gardnernella vaginalis
II. Hepatitis G

The use of the following nucleic acid testing panel (without quantification of viral load) may be considered medically necessary:
I. Respiratory Virus Panel

The use of the following nucleic acid testing panels (with or without quantification of viral load for viral panel elements) is considered investigational:
I. Central nervous system pathogen panel
II. Gastrointestinal pathogen panel</td></tr>
</table>

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