2.04.10	Identification of Microorganisms Using Nucleic Acid Probes		
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Section:	2.0 Medicine	**Page:**	Page 1 of 52

Policy Statement

I. 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):
   A. Bartonella henselae or quintana
   B. Bordetella pertussis
   C. Candida species
   D. Chlamydia pneumoniae
   E. Chlamydia trachomatis
   F. Clostridium difficile
   G. Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
   H. Enterovirus
   I. Herpes simplex virus
   J. Human papillomavirus
   K. Influenza virus
   L. Legionella pneumophila
   M. Mumps
   N. Mycobacterium species
   O. Mycobacterium tuberculosis
   P. Mycobacterium avium-intracellulare
   Q. Mycoplasma pneumoniae
   R. Neisseria gonorrhoeae
   S. Rubeola (measles)
   T. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
   U. Staphylococcus aureus
   V. Staphylococcus aureus, methicillin-resistant
   W. Streptococcus, group A
   X. Streptococcus, group B
   Y. Trichomonas vaginalis
   Z. Zika virus

II. 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:
   A. Cytomegalovirus
   B. Hepatitis B virus
   C. Hepatitis C virus
   D. Human herpesvirus 6
   E. Human Immunodeficiency Virus 1 (HIV-1)
   F. Human Immunodeficiency Virus 2 (HIV-2)

III. 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.

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

B. Hepatitis G

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

VI. The use of the following nucleic acid testing panels (*with or without* quantification of viral load for viral panel elements) is considered **investigational**:
   A. Central nervous system pathogen panel
   B. Gastrointestinal pathogen panel

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

Policy Guidelines

Vaccine-preventable disease surveillance for outbreaks and diagnosis of isolated cases: the Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory has developed its own polymerase chain reaction (PCR) and serological assays to diagnose pertussis, mumps, and rubeola (measles) and has recommendations for their appropriate use.

For bacterial vaginosis, this evidence review addresses the use of single organism direct or amplified nucleic acid probes with or without quantification.

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 culture 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 nucleic acid amplification tests (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 individuals, 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 individuals 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

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 represents Bartonella ddPCR, Galaxy Diagnostics Inc. Per the manufacturer, this is a MAAA test for Bartonellosis, cat scratch disease, trench fever, Bartonella endocarditis, Bartonella arthritis, neurobartonellosis, peliosis hepatitis, splenomegaly, bacillary angiomatosis, neuroretinitis, peripheral neuropathy.

- **0301U:** Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR);

There is a CPT code that represents Bartonella Digital ePCR™, Galaxy Diagnostics Inc. Per the manufacturer, this is a MAAA test for Bartonellosis, cat scratch disease, trench fever, Bartonella

endocarditis, Bartonella arthritis, neurobartonellosis, peliosis hepatitis, splenomegaly, bacillary angiomatosis, neuroretinitis, peripheral neuropathy.

- **0302U:** Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); following liquid enhancement

The following PLA code represents a panel used to diagnose meningitis/ encephalitis caused by a broad range of pathogenic organisms (e.g., bacteria, fungi, DNA or RNA viruses, parasites). It may have been previously billed using 81479.

- **0323U:** Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi

The following PLA code is for a test detects the presence of multiple organisms known to be associated with a variety of vaginal infections.

- **0330U:** Infectious agent detection by nucleic acid (DNA or RNA), vaginal pathogen panel, identification of 27 organisms, amplified probe technique, vaginal swab

Effective April 1, 2023, the following PLA code is for GI assay (Gastrointestinal Pathogen with ABR), Lab Genomics LLC, Thermo Fisher Scientific. Per the manufacturer, the test would be indicated for individuals showing symptoms of diarrhea, acute or chronic graft versus host disease, cytokine release syndrome, food poisoning, immunoglobulin deficiency, fever, Di George Syndrome, Crohn's disease, Mast Cell activation, compromised immune system or with recurring GI infection.

- **0369U:** Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique

The following is a Category I code created to report infectious agent antigen detection for blood stream pathogens. It may have been previously reported with multiple units of a code according to the number of pathogens (e.g., 87150)

- **87154:** Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets

Effective January 1, 2023, these codes were established to identify the infectious agent detection by nucleic acid using an amplified probe technique for identification of the specific tick-borne bacteria.

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

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 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])

There are two 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

There is a 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	

Pathogen	Direct Probe	Amplified Probe	Quantification
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
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, microbial identification using standard culture is difficult or impossible, and/or 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

The U.S. Food and Drug Administration maintains a list of nucleic acid amplification tests (NAATs) that have been cleared by the Center for Devices and Radiological Health. These NAATs have been cleared for many of the microorganisms discussed in this review and may be reviewed on this site.

Table 1 summarizes the NAATs cleared for central nervous system panels when diagnosing meningitis and/or encephalitis, for panels when diagnosing gastroenteritis, and for respiratory panels.

Table 1. FDA Cleared Nucleic Acid Amplification Tests for Central Nervous System, Gastrointestinal, and Respiratory Panels

NAAT	Manufacturer	510(k) Number	Product Code
Meningitis/Encephalitis (CNS) Pathogen Panels			
FilmArray Meningitis/Encephalitis Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	DEN150013, K160462	PLO
Gastroenteritis Pathogen Panels			
xTAG Pathogen Panel (GPP)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	DEN130003, K121454	PCH
Progastro SSCS Assay	Gen-Probe Prodesse, Inc (Waukesha, WI)	K123274	PCH
Biocode Pathogen Panel	Applied Biocode (Santa Fe Springs, CA)	K190585	PCH
EntericBio Dx Assay	Serosep, Ltd (Annacotty, IE)	K182703	PCH
Filmarray Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	K140407, K160459	PCH
ProGastro SSCS	Hologic/Genprobe (Waukesha, WA)	K123274	PCH
BD MAX Enteric Bacterial Panel (EBP)	BD Diagnostics (Sparks, MD)	K170308	PCH
Verigene Enteric Pathogen Panel (EP)	Nanosphere, Inc (Northbrook, IL)	K142033, K140083	PCH
xTAG Gastroenterology Pathogen Panel (GPP) Multiplex Nucleic Acid-Based Assay System	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K121894	PCH
FilmArray GI Panel	BioFire Diagnostics, Inc (Salt Lake City, UT)	K140407	PCH
Respiratory Viral Panels			
ID-TAG Respiratory Viral Panel Nucleic Assay System	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	DEN070013, K063765	OCC
Biocode Respiratory Pathogen Panel	Applied BioCode, Inc. (Santa Fe Springs, CA)	K192485	OCC
Nxtag Respiratory Pathogen Panel	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K193167	OCC
xTAG Respiratory Virus Panel (RVP)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K081483	OCC
Qiastat-Dx Respiratory Panel	QIAGEN GmbH (Germantown, MD)	K183597	OCC
xTAG Respiratory Virus Panel FAST	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K103776	OCC
eSensor® Respiratory Virus Panel (RVP)	Clinical Micro Sensors, Inc (Carlsbad, CA)	K113731	JJH
Verigene Respiratory Pathogens Plus Nucleic Acid Test	Nanosphere, Inc (Northbrook, IL)	K103209	OCC
BioFire FilmArray Respiratory Panel (RP)	BioFire Diagnostics, Inc (Salt Lake City, UT)	K123620	OCC

CNS: central nervous system; DEN: de novo; FDA: Food and Drug Administration; NAAT: nucleic acid amplification tests.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing.

Rationale

Background

Nucleic Acid Probes

A nucleic acid probe is used to detect and identify species or subspecies of organisms by identifying nucleic acid sequences in a sample. Nucleic acid probes detect genetic materials, such as RNA or DNA, unlike other tests, which use antigens or antibodies to diagnose organisms.

The availability of nucleic acid probes has permitted the rapid direct identification of microorganism DNA or RNA. Amplification techniques result in exponential increases in copy numbers of a targeted strand of microorganism-specific DNA. The most used amplification technique is polymerase chain reaction (PCR) or reverse transcriptase PCR. In addition to PCR, other nucleic acid amplification techniques have been developed, such as transcription-mediated amplification, loop-mediated isothermal DNA amplification, strand displacement amplification, nucleic acid sequence-based amplification, and branched-chain DNA signal amplification. After amplification, target DNA can be readily detected using a variety of techniques. The amplified product can also be quantified to assess how many microorganisms are present. Quantification of the number of nucleic acids permits serial assessments of response to treatment; the most common clinical application of quantification is the serial measurement of HIV RNA (called viral load).

The direct probe technique, amplified probe technique, and probe with quantification methods vary based on the degree to which the nucleic acid is amplified and the method for measurement of the signal. The direct probe technique refers to detection methods in which nucleic acids are detected without an initial amplification step. The amplified probe technique refers to detection methods in which either target, probe, or signal amplification is used to improve the sensitivity of the assay over direct probe techniques, without quantification of nucleic acid amounts.

- Target amplification methods include PCR (including PCR using specific probes, nested or multiplex PCR), nucleic acid-based sequence amplification, transcription-mediated amplification, and strand displacement amplification. Nucleic acid-based sequence amplification and transcription-mediated amplification involve amplification of an RNA (rather than a DNA) target.
- Probe amplification methods include ligase chain reaction.
- Signal amplification methods include branched DNA (bDNA) probes and hybrid capture methods using an anti-DNA/RNA hybrid antibody.

The probe with quantification techniques refers to quantitative PCR or real-time PCR methods that use a reporter at each stage of the PCR to generate absolute or relative amounts of a known nucleic acid sequence in the original sample. These methods may use DNA-specific dyes (ethidium bromide or SYBR green), hybridization probes (cleavage-based [TaqMan] or displaceable), or primer incorporated probes.

Direct assays will generally have lower sensitivity than amplified probes. In practice, most commercially available probes are amplified, with a few exceptions. For this evidence review, indications for direct and/or amplified probes without quantification are considered together, while indications for a probe with quantification are considered separately.

Classically, identification of microorganisms relies either on the culture of body fluids or tissues or identification of antigens, using a variety of techniques including direct fluorescent antibody

technique and qualitative or quantitative immunoassays. These techniques are problematic when the microorganism exists in very small numbers or is technically difficult to culture. Indirect identification of microorganisms by immunoassays for specific antibodies reactive with the microorganism is limited by difficulties in distinguishing between past exposure and current infection.

Potential reasons for a nucleic acid probe to be associated with improved clinical outcomes compared with standard detection techniques include the following (note: in all cases, for there to be clinical utility, making a diagnosis should be associated with changes in clinical management, which could include initiation of effective treatment, discontinuation of other therapies, or avoidance of invasive testing):

- Significantly improved speed and/or efficiency in making a diagnosis.
- Improved likelihood of obtaining any diagnosis in cases where standard culture is difficult. Potential reasons for difficulty in obtaining standard culture include low numbers of the organisms (e.g., HIV), fastidious or lengthy culture requirements (e.g., *Mycobacteria, Chlamydia*, *Neisseria* species), or difficulty in collecting an appropriate sample (e.g., herpes simplex encephalitis).
- There is no way to definitively make a diagnosis without nucleic acid testing.
- The use of nucleic acid probe testing provides qualitatively different information than that available from standard cultures, such as information regarding disease prognosis or response to treatment. These include cases where quantification of viral load provides prognostic information or is used to measure response to therapy.

The risks of nucleic acid testing include false-positive and false-negative results, inaccurate identification of pathogens by the device, inaccurate interpretation of test results, or incorrect operation of the instrument.

- False-positive results can lead to unnecessary treatment, with its associated toxicities and side effects, including allergic reaction. In addition, true diagnosis and treatment could be delayed or missed altogether.
- False-negative results could delay diagnosis and initiation of proper treatment.
- It is possible that these risks can be mitigated by the use of a panel of selected pathogens indicated by the clinical differential diagnosis while definitive culture results are pending.

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. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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 Diseases Society of America, or America Academy of Pediatrics were used to evaluate appropriate indications for the following individual microorganisms: *Bartonella henselae or quintana, Candida* species, *Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium difficile,* cytomegalovirus, enterovirus, hepatitis B virus, hepatitis C virus, 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, vancomycin-resistant *Enterococcus,* and 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 a nucleic acid-based CNS pathogen panel 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.

Populations

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

Interventions

The test being considered is nucleic acid-based CNS pathogen panel.

Testing with a CNS pathogen panel leads to reduced time to diagnosis compared with standard laboratory techniques (approximately 1 to 8 hours).[1,]

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 cerebrospinal fluid (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 meningitidis*; *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.

Comparators

Comparators of interest include culture or serologic tests and CNS pathogen-specific testing (nucleic acid-based testing for individual pathogens).

The standard approach to the diagnosis of meningitis and encephalitis is culture and pathogen-specific polymerase chain reaction (PCR) testing of 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.

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 the receiver operating characteristic curve [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.

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 types 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	Sensitivity, 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 to 93.1	94.6 to 99.0	NR	NR	NR	NR	NR	NR
Range	60 to 100	88 to 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 an FDA pivotal study, as well as the largest and 1 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 (Table 3). 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) of 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 (Table 4). The investigators suggested that the discrepancies could have been due to specimen contamination or another problem with the assay configuration or testing process.

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 meningitidis				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						
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 influenzae				1.5	100 (48 to 100)	100 (97 to 100)
Listeria monocytogenes				0	NA	100 (98 to 100)
Neisseria meningitidis				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-zoster virus				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]

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.

Tables 5 and 6 display notable limitations identified in each study.

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				

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.
[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).

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	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Graf et al (2017)[4,]	2. 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

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.

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, more effective therapy, or avoid unnecessary therapy, or 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).

No RCTs were available that evaluated clinical utility.

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 diagnostic option that is an alternative to or an improvement on existing tests in patients with signs and/or symptoms of gastroenteritis.

The question addressed in this evidence review is: Does testing for microorganisms using a nucleic acid-based GI pathogen panel improve the net health outcome in individuals with signs and/or symptoms of gastroenteritis?

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

Populations
The relevant population of interest is individuals with signs and/or symptoms of gastroenteritis.

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, Clostridioides (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 GI pathogen 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* (ETEC), Shiga toxin-producing *E coli* (STEC), *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), STEC, and *E coli* O157. More pathogen targets may be included if testing for *C difficile* or testing patients who are critically ill or immunocompromised.[10,]

Time to a result of testing with a pathogen panel is reduced compared with standard laboratory techniques (<6 hours).[11,]

Comparators
Comparators of interest include culture or serologic tests and GI pathogen-specific testing (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,]

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.

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.

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 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).[13,]

Table 7. Prospective Performance Data by Organism

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

Source: FDA Decision Summary.[13,]
CI: Confidence interval; ETEC: enterotoxigenic *Escherichia coli;* STEC: Shiga toxin–producing *E coli.*

Several studies of GI pathogen 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 Pathogen Panel (GPP; Luminex, Toronto, ON, Canada) compared with traditional diagnostic methods (i.e., culture, microscopy, enzyme immunoassay/ direct fluorescent antibody, real-time PCR , or sequencing) using 901 stool samples from multiple sites.[14,] The sensitivity of GPP against real-time PCR was >90% for nearly all pathogens tested by real-time PCR; the 1 exception was adenovirus at 20%, but sensitivity could be higher because real-time PCR 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 xT AG GPP.[15,] 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 xT AG detected 69 (30.3%). Two of the most commonly detected pathogens in both assays were *C difficile* (12.6% to 13.9% prevalence) and norovirus (5.7% to 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 difficile, Salmonella* species, *Cryptosporidium,* and *Giardia lamblia.* Specificity was >90% for all but norovirus (42%) and *G lamblia* (56%); 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 (NPV) was 100% for all pathogens.

Buchan et al (2013) evaluated a multiplex real-time PCR assay (ProGastro SSCS, Gen-Probe Prodesse, San Diego, CA) limited to *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. against culture; and they tested for 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 NPV.

Jiang et al (2014) developed a reverse transcription and multiplex real-time PCR assay to identify 5 viruses in a single reaction.[18,] The viruses included norovirus genogroups I and II; sapovirus genogroups I, II, IV, and V; human rotavirus A; adenovirus serotypes 40 and 41; and human astrovirus. Compared with monoplex real-time PCR, multiplex real-time PCR 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 studies included patients with acute diarrhea, compared multiplex GI pathogen panel 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 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

an assessment of GI panel testing effect on patient management and outcomes, compared with conventional testing, is needed.

Kosai et al (2021) evaluated the Verigene Pathogens Nucleic Acid Test (Luminex Corporation), testing 268 clinical stool samples for bacteria and toxins and 167 samples for viruses.[20,] Of these samples, 256 and 160 samples, respectively, (95.5% and 95.8%) had fully concordant results between the Verigene EP test and the reference methods (which were culture for bacteria and toxins and xTAG GPP for viral detection). Overall sensitivity and specificity were 97.0% and 99.3%, respectively. Sensitivity for individual pathogens ranged from 87.5% to 100%, and specificity ranged from 98.7% to 100%. A total of 13 false-positive and 6 false-negative results were reported.

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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

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[21,] (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 rather than empirical therapy (r^2=0.65; p=.009 by linear regression). Results of the GI panels resulted in discontinuation of antimicrobials in 8 of 9 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 were tested with both a GI panel and culture.

The prospective study by Beal et al (2017) also aimed to assess the clinical impact of the BioFire FilmArray GI panel[22,] (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). The GI panel patients had significantly fewer subsequent infectious stool tests compared with the control group. The 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 limitations of the study include not confirming the results in which the GI panel did not agree with standard testing and using a historical cohort as a control group.

Table 8. Summary of Key Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Test 1	Test 2
Cybulski et al (2018)[21,]	Prospective multi-center, parallel design	U.S.	Jan-Sep 2017 (controls from 2016)	Newly admitted inpatients (<3 d) and outpatients aged 0 to 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 et al (2017)[22,]	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; U.S.: United States

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)[21,]		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)[22,]		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 to 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.

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 respiratory infection.

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

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

Populations

The relevant population of interest is individuals with signs and/or symptoms of respiratory infections.

The available evidence also notes that respiratory pathogen panels are particularly effective for high-risk individuals.

High-risk individuals can include:

- Immunocompromised adult or pediatric patients, such as
  - Hematopoietic stem cell or solid organ transplant recipients
  - Individuals receiving high-dose chemotherapy and/or steroids
- Adults who appear acutely ill with respiratory conditions—particularly in certain settings such as influenza outbreaks
- Critically ill adult individuals—particularly intensive care unit (ICU) patients

Interventions

The test being considered is the nucleic acid-based respiratory pathogen panel.

The respiratory pathogen 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*.

Comparators

Comparators of interest include culture or serologic tests and respiratory pathogen-specific testing (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.

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.

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

Huang et al (2018) published a systematic review and meta-analysis of a multiplex PCR system for the rapid diagnosis of respiratory virus infections.[23,] 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 except 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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

Several studies of various respiratory viral panels have demonstrated that 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.[24,25,26,]

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[27,] (Table 10). 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 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[28,] (Table 10). 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% confidence interval [CI], -24.8% to -1.7%; p=.0289). Mean test turnaround time for POCT was 2.3 hours (standard deviation [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	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Andrews et al (2017)[a27,]	United Kingdom	1	Jan-Jul 2015	Patients with influenza-like illness/upper RTI +/- lower RTI N=454	FilmArray POCT (even days of month) n=334	Routine, laboratory-based respiratory panel PCR testing +/- atypical serology (odd days) n=211
Brendish et al (2017)[28,]	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 discretion n=358

ED: emergency department; PCR: polymerase chain reaction; POCT: point of care testing (using FilmArray Respiratory Panel); RCT: randomized controlled trial; 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."

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)[27],		Median (IQR)	Median (IQR)		
Active	24%	98.6 h (48.1 to 218.4)	6.0 d (4.0 to 7.0)	4%	19%
Comparator	20%	79.6 h (41.9 to 188.9)	6.8 d (5.0 to 7.3)	4%	20%
Estimated intervention effect	NR	NR	Absolute difference in natural logarithm of duration: -0.08 (95% CI: -0.22 to 0.054)	OR: 0.9 (95% CI, 0.3 to 2.2)	OR: 0.9 (95% CI, 0.6 to 1.4)
Adjusted p value	NR	NR	.23	.79	.70
Brendish et al (2017)[28],		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 to 0.4)[c]	-2.0% (-4.7% to 0.6%)	-3.0% (-8.3% to 2.0%)
OR (95% CI)	NR	NR	0.95 (0.85 to 1.05)[d]	0.54 (0.3 to 1.2)	0.78 (0.5 to 1.2)
p value	NR	.04	.32	.15	.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.

Tables 12 and 13 display notable limitations identified in each study.

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)[27],	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)[28],		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 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 with other tests not reported.

Table 13. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Andrews et al (2017)[27,]	4. Patients were not noted to be high-risk				
Brendish et al (2017)[28,]				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 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.
[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).

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 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 CNS 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 CSF. The available CNS 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 that the technology results in an improvement in the net health outcome.

For individuals who have signs and/or symptoms of gastroenteritis who receive a nucleic acid-based GI 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 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 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 that the technology results in an improvement in the net health outcome.

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 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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	AAP (5.1), CDC (1.5.1)[b]	IDSA (3.1, 3. 6)
CNS pathogen panel	IDSA (3.2, 3.3)	NA
Chlamydia pneumoniae	AAP (5.1), CDC (1.5.3), IDSA (3.1[c])	NA
Chlamydia trachomatis	CDC (1.5.2,[c] 1.6[c]), IDSA (3.1), AAP (5.1)	NA
Clostridioides (Clostridium) difficile	NIH (2.1.2), AAP (5.1)	IDSA (3.1, 3.4)
Cytomegalovirus	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

Microorganism	Guidelines Recommending the Use of NAATs (Location)	Guidelines Not Recommending the Use of NAATs[a] (Location)
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 (3.2)
***Mycobacteria* species**	CDC (1. 7), 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
Respiratory panel	None Identified	NA
SARS-CoV-2	IDSA (3. 7)	NA
Staphylococcus aureus	IDSA (3.1), AAP (5.1)	NA
***Streptococcus*, group A**	IDSA (3.1)	AAP (5.1)
***Streptococcus*, group B**	AAP (5.2), ASM (7.1)	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 virus	CDC (1.3), IDSA (3.1), AAP (5.1)	NA

AAP: American Academy of Pediatrics; ACG: American College of Gastroenterology; ASM: American Society for Microbiology; AST: American Society of Transplantation; CDC: Centers for Disease Control and Prevention; CNS: central nervous system; GI: gastrointestinal; HIV: human immunodeficiency virus; IDSA: Infectious Disease Society of America; NA: not applicable (none found); NAAT: nucleic acid amplification test; NIH: National Institutes of Health; SARS-CoV-2: *Severe acute respiratory syndrome coronavirus 2*.

[a] Guidelines Not Recommending includes not only guidelines that recommend against 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.

Centers for Disease Control and Prevention

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

1.1 The CDC published guidance for laboratory testing for cytomegalovirus (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.[29,]

1.2 The CDC published diagnostic methods for mycoplasma pneumoniae.[30,] They cited NAAT as a method of diagnosis, along with culture or serology.

1.3 The CDC published updated guidelines on Zika virus testing.[31,]Routine testing for Zika virus in asymptomatic pregnant patients is not recommended, but NAAT testing may still be considered for asymptomatic pregnant women with recent travel to an area with risk of Zika outside the U.S. and its territories. Symptomatic pregnant patients should receive NAAT testing if they have recently traveled to areas with a risk of Zika virus or if they have had sex with someone who lives in or recently traveled to areas with risk of Zika virus. If a pregnant woman (with risk of Zika virus exposure) has a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection, Zika virus NAAT and IgM testing should be performed on maternal serum and NAAT on maternal urine. If amniocentesis is being performed as part of clinical care, Zika virus NAAT testing of amniocentesis specimens should also be performed.

1.4 In 2017, the CDC updated its guidelines on norovirus gastroenteritis outbreak management and disease prevention.[32,33,] 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.

1.5 In 2015, the CDC made recommendations for the use in NAATs in diagnosing numerous sexually transmitted infections. [34,]These recommendations were most recently updated in 2021, with the publication of new guidelines and the following recommendations:[35,]

1.5.1 For *Candida* species:
- "The majority of PCR tests for yeast are not FDA [U.S. Food and Drug Administration] cleared, and providers who use these tests should be familiar with the performance characteristics of the specific test used."

1.5.2 For Gonococcal Infections:
- "Culture, NAAT, and POC [point of care] NAAT, such as GeneXpert (Cepheid), are available for detecting genitourinary infection with *N. gonorrhoeae*"
- "NAATs and POC NAATs allow for the widest variety of FDA-cleared specimen types, including endocervical and vaginal swabs and urine for women, urethral swabs and urine for men, and rectal swabs and pharyngeal swabs for men and women. However, product inserts for each NAAT manufacturer should be consulted carefully because collection methods and specimen types vary."

1.5.3 For Chlamydial Infection:
- "NAATs are the most sensitive tests for these specimens and are the recommended test for detecting *C. trachomatis* infection. NAATs that are FDA cleared for use with vaginal swab specimens can be collected by a clinician or patient in a clinical setting. Patient collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs, and this screening strategy is highly acceptable among women. Optimal urogenital specimen types for chlamydia screening by using NAAT include firstcatch urine (for men) and vaginal swabs (for women). Recent studies have demonstrated that among men, NAAT performance on self-collected meatal swabs is comparable to patient-collected urine or provider-collected urethral swabs."

1.5.4 For *Gardnerella vaginalis*:
- "Multiple BV [bacterial vaginosis] NAATs are available for BV diagnosis among symptomatic women. These tests are based on detection of specific bacterial nucleic acids and have high sensitivity and specificity for BV (i.e., *G. vaginalis, A. vaginae*, BVAB2, or Megasphaera type 1) and certain lactobacilli (i.e., *Lactobacillus crispatus, Lactobacillus jensenii*, and *Lactobacillus gasseri*)...Five quantitative multiplex PCR assays are available...Two of these assays are FDA cleared (BD Max Vaginal Panel and Aptima BV), and the other three are laboratory-developed tests."

1.5.5 For hepatitis C infection (HCV):
- 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. Persons with HIV infection with low CD4+ T-cell count might require further testing by NAAT because of the potential for a false-negative antibody assay."

1.5.6 For diseases characterized by genital, anal, or perianal ulcers (e.g., herpes simplex virus [HSV], syphilis):
- "Specific evaluation of genital, anal, or perianal ulcers includes syphilis serology tests and darkfield examination from lesion exudate or tissue, or NAAT if available; NAAT or culture for genital herpes type 1 or 2; and serologic testing for type-specific HSV antibody. In settings where chancroid is prevalent, a NAAT or culture for *Haemophilus ducreyi* should be performed;" and

- "PCR is also the test of choice for diagnosing HSV infections affecting the central nervous system (CNS) and systemic infections (e.g., meningitis, encephalitis, and neonatal herpes). HSV PCR of the blood should not be performed to diagnose genital herpes infection, except in cases in which concern exists for disseminated infection (e.g., hepatitis)."

1.5.7 For *Human immunodeficiency virus 1* (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.

1.5.8 For human papillomavirus (HPV):

- 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;
- Testing for nononcogenic HPV (types 6 and 11) 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;" when "providing care to persons with genital warts or their partners;" when "testing persons aged <25 years as part of routine cervical cancer screening;" or when "testing oral or anal specimens."

1.5.9 For *Trichomonas vaginalis*:

- NAAT is recommended for detecting *T vaginalis* in women due to its high sensitivity and specificity. Multiple assays are FDA-cleared to detect *T vaginalis* from vaginal, endocervical, or urine specimens for women.
- Although there is not a currently FDA-cleared assay test available for use in men, assays "...should be internally validated in accordance with CLIA [Clinical Laboratory Improvement Amendments] regulations before use with urine or urethral swabs from men."

1.6 In 2014, the CDC published recommendations regarding the laboratory-based detection of *C. trachomatis* and *N. gonorrhoeae* infections.[36,] 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* should be used "as screening or diagnostic tests because they have been evaluated in patients with and without symptoms."

1.7 In 2009, the CDC published updated guidelines for the use of NAATs in diagnosing *Mycobacterium tuberculosis* bacteria.[37,] The CDC recommended that "NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB [tuberculosis] 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 to 2 weeks to 1 to 2 days."

National Institutes of Health et al

2.1 The National Institute of Health (NIH), CDC, and HIV Medicine Association of the Infectious Diseases Society of America (IDSA) published guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV.[38,]The most recent update took place in 2022. In these guidelines, NAATs are discussed in the following situations:

2.1.1 *Bartonella* species

- For patients with suspected bacillary angiomatosis, serologic tests are the standard of care and the most accessible test for diagnosing Bartonella infection. There are PCR methods that have been developed for identification and speciation of *Bartonella*and are becoming increasingly available through private laboratories, as well as the CDC and may aid in diagnosis of *Bartonella* in freshly biopsied tissue samples or whole blood.

2.1.2 *Clostridioides (Clostridium) difficile*

- Detection of either the *C. difficile* toxin B gene, using NAAT, or the *C. difficile* toxin B protein, using an enzyme immunoassay, is required for diagnosis. PCR assays have high sensitivity and can detect asymptomatic carriers.

2.1.3 Cytomegalovirus

- For patients with suspected CMV disease, diagnosis is based on clinical symptoms and the presence of CMV in cerebral spinal fluid (CSF) or brain tissue, most often evaluated with PCR. "Viremia can be detected by PCR" however, "a negative serum or plasma PCR assay does not rule out CMV end-organ disease."

2.1.4 Hepatitis B

- The CDC, the United States Preventive Services Task Force, and the American Association for the Study of Liver Disease (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.

2.1.5 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.

2.1.6 Herpes Simplex Virus

- "HSV DNA PCR and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV."

2.1.7 *Mycobacterium tuberculosis* infection and disease

- " NAA tests provide rapid diagnosis of TB, and some assays also provide rapid detection of drug resistance."
- "NAA assays, if positive, are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because nontuberculous mycobacterial infections (NTM) may occur in people with HIV with advanced immunodeficiency, negative NAA results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct therapy and make decisions about the need for respiratory isolation."
- "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. NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens."

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.

3.1 In 2018, the IDSA and the American Society for Microbiology published a guide on the diagnosis of infectious diseases.[39,] In this guideline, NAATs were recommended diagnostic procedures for enterovirus, hepatitis C, hepatitis B, cytomegalovirus, herpes simplex virus, human herpesvirus 6, HIV, influenza virus, and Zika virus. For bacterial vaginosis, NAATs were not recommended diagnostic procedures. 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 acrimal and eyelid infections; proctitis; epididymitis and orchitis; pathogens associated with cervicitis/ urethritis; pathogens associated with pelvic inflammatory disease and endometritis
Clostridioides (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 periorbital cellulitis, and acrimal and eyelid infections; periocular structure infections/ keratitis; pharyngitis; genital lesions
HIV	Pericarditis and myocarditis; meningitis[c]; pharyngitis[c]
Human herpesvirus 6	Encephalitis
Influenza virus	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; MRSA: 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.

Use of NAATs for diagnosing *Candida* species, *Gardnerella vaginalis*, *Streptococcus* group B, and vancomycin-resistant *Enterococcus* as etiologic agents was not recommended.

3.2 In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis.[40,] 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).

3.3 In 2008, the IDSA published clinical practice guidelines for the management of encephalitis.[41,] 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."[42,])
- "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."[42,])
- "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 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, herpes simplex virus 1 and 2, human herpesvirus 6, *Bartonella henselae*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*.

3.4 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 *Clostridioides (Clostridium) difficile*.[43,]

- "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."

3.5 In 2017, the IDSA published clinical practice guidelines for the diagnosis and management of infectious diarrhea.[44,] 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 *Clostridioides (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 CMV.
- 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).

3. 6 In 2016, the IDSA published updated clinical practice guidelines for managing candidiasis.[45,] 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."

3. 7 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, 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 coronavirus disease 2019 (COVID-19) diagnosis guideline using the 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 recommendations will require frequent updating.[46,] The current recommendations (published December 23, 2020) support *Severe acute respiratory syndrome coronavirus 2* (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 with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community;
- asymptomatic individuals who are immunocompromised and being admitted to the hospital, regardless of COVID-19 exposure;
- asymptomatic individuals prior to hematopoietic stem cell transplant or solid organ transplantation, regardless of COVID-19 exposure;
- asymptomatic individuals without known exposure to COVID-19 undergoing major time-sensitive surgeries;
- asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when personal protective equipment (PPE) is limited, and testing is available;
- asymptomatic individuals without known exposure when the results will impact isolation/quarantine/ PPE usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy.

The IDSA panel further recommends the following:

- collecting nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than oropharyngeal swabs alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection or influenza like illness suspected of having COVID-19 (conditional recommendation, very low certainty of evidence).
- nasal and mid-turbinate 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 or influenza like illness 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).
- using either rapid reverse-transcriptase (RT)-PCR or standard laboratory-based NAATs over rapid isothermal NAATs in symptomatic individuals suspected of having COVID-19 (conditional recommendation, low certainty of evidence).

American Society of Transplantation

4.1 In 2019, the American Society of Transplantation Infectious Diseases Community of Practice published guidelines which addressed vancomycin-resistant enterococci (VRE) infections in solid organ transplant patients.[47,] 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

5.1 The thirty-second edition of the American Academy of Pediatrics (AAP) Red Book (2021) describes the diagnostic and treatment options for many infectious diseases in the pediatric population.[48,] Their recommendations for appropriate diagnostic tests for the viruses and infections discussed in this policy are detailed in Table 16.

Table 16. Red Book Diagnostic Test Recommendations for the Pediatric Population

Infection	Diagnostic Test Recommendation
Bartonella henselae	EIA IFA NAAT (PCR)
Candida species	Clinical evaluation microscopy PNA FISH probes and PCR assays developed for rapid detection directly from positive blood cultures
Chlamydia pneumoniae	NAATs (PCR) are the preferred method for diagnosis of acute infection Serologic antigen test is an option, but is technically complex and interpretation is subjective
Chlamydia trachomatis	NAATs are recommended for *C trachomatis* urogenital infections and in postpubescent individuals. They are not recommended for diagnosing *C trachomatis* conjunctivitis or pneumonia or in the evaluation of prepubescent children for possible sexual assault.
Clostridioides (Clostridium) difficile	NAATs detect genes responsible for the production of toxins A and B, rather than free toxins A and B in the stool, which are detected by EIA NAAT could be considered alone if a policy in place to screen symptoms; if no policy in place, multi-step algorithms involving EIA, GDH, NAAT plus toxin is recommended
Coronaviruses (including SARS-CoV-2 and MERS-CoV)	RT-PCR Direct antigen testing
Cytomegalovirus	Saliva PCR is the preferred diagnostic tool for screening.
Enterovirus	RT-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

Infection	Diagnostic Test Recommendation
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 or RNA PCR- preferred test to diagnose HIV infection in infants and children younger than 18mo; highly sensitive and specific by 2 weeks of age and available
Human papillomavirus	"Detection of HPV infection is based on detection of viral nucleic acid."
Influenza virus	RT-PCR, viral culture tests, and rapid influenza molecular assays are available options for testing; optimal choice of influenza test depends on the clinical setting.
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 Several NAATs are cleared for rapid detection of *M tuberculosis,* but expert consultation is recommended for interpretation of results NTM: "definite diagnosis of NTM disease requires isolation of the organism."
Mycoplasma pneumoniae	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 group A streptococcal infection…Laboratory confirmation before initiation of antimicrobial treatment is required for cases in children without viral symptoms… culture on sheep blood agar can confirm group A streptococcal infection."
***Streptococcus*, group B**	"Gram-positive cocci in pairs or short chains from a normally sterile body fluid provides 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*	"Selective agars are available for screening of vancomycin-resistant enterococcus from stool specimens. Molecular

Infection	Diagnostic Test Recommendation
	assays are available for direct detection of *vanA* and *vanB* genes from rectal and blood specimens to identify vancomycin-resistant enterocci"
Zika virus	NAATs Trioplex real-time PCR assay Serologic testing

BCYE: buffered charcoal yeast extract; CNS: central nervous system; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; EIA: enzyme immunoassay; FDA: Food and Drug Administration; GDH: glutamate dehydrogenase; HIV: human immunodeficiency virus; HPV: human papillomavirus; HSE: herpes simplex encephalitis; IFA: indirect fluorescent antibody; MERS-CoV: Middle East respiratory syndrome coronavirus; MSRA: methicillin-resistant *Staphylococcus aureus*; NAAT: nucleic acid amplification test; NTM: nontuberculous mycobacteria; PCR: polymerase chain reaction; PNA FISH: peptide nucleic acid fluorescent in situ hybridization; RNA: ribonucleic acid; RT: reverse transcriptase; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

5.2 In 2019, the AAP published guidelines on managing infants at risk for group B streptococcus (GBS).[49,] 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

6.1 In 2016, the American College of Gastroenterology published clinical guidelines on the diagnosis, treatment, and prevention of acute diarrheal infections in adults.[50,] 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.

American Society for Microbiology

7.1 In 2020, the American Society for Microbiology updated the 2010 guidelines on detecting and identifying GBS that were originally published by the CDC, with plans to continue updating regularly.[51,]The most recent update took place July 2021. The guidelines state that "intrapartum NAAT without enrichment has an unacceptably high false negative rate...As such we do not recommend the use of intrapartum NAAT without enrichment to rule out the need for prophylaxis." All GBS screening specimens should be incubated in selective enrichment broth prior to agar media plating or NAAT. "Nucleic acid amplification-based identification of GBS from enrichment broth is acceptable" for GBS screening, "but not sufficient for all patients" due to high false-negative rates.

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.

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			
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	Apr 2022
NCT03362970[a]	Improvements Through the Use of a Rapid Multiplex PCR Enteric Pathogen Detection Kit in Children With Hematochezia	60	Dec 2022
NCT03840603[a]	PROARRAY: Impact on PCT+ FilmArray RP2 Plus Use in LRTI Suspicion in Emergency Department	444	Dec 2021
NCT04835818	Clinical Impact on Point-of-Care Multiplex Polymerase Chain Reaction (PCR) Testing for Critically Ill Adult Patients With Community-acquired Pneumonia	60	May 2022
NCT04651712	The Effect of a Point-of-care Sputum Specimen Assay on Antibiotic Treatment of Patients Admitted Acutely With Suspected Pneumonia: A Multicenter Randomized Controlled Trial	200	Jul 2022
NCT04547556[a]	ADEQUATE Advanced Diagnostics for Enhanced QUality of Antibiotic Prescription in Respiratory Tract Infections in Emergency Rooms	1600	Jun 2023
NCT04781530[a]	ADEQUATE Advanced Diagnostics for Enhanced QUality of Antibiotic Prescription in Respiratory Tract Infections in Emergency Rooms - Paediatric	900	Jun 2023
NCT04660084	Impact of Molecular Testing on Improved Diagnosis, Treatment and Management of CAP in Norway: a Pragmatic Randomised Controlled Trial	1060	Dec 2022
NCT03809117[a]	A Randomized Controlled Trial of Biofire Film Array Panel Compared to Usual Care for Evaluation of Acute Infectious Diarrhea in the Emergency Department	176	Nov 2019
ISRCTN16483855	The impact of using film array pneumonia panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK critical care: a multicentre randomised controlled trial and a COVID-19 related observational sub-study	558	Apr 2022
Unpublished			
NCT03895281[a]	Clinical Evaluation of the FilmArray® Meningitis/Encephalitis (ME) Panel	150	Apr 2020 (Unknown)

ISRCTN: International Standard Randomised Controlled Trial Number; NCT: national clinical trial.
[a]Denotes industry-sponsored or cosponsored trial

References

1. He T, Kaplan S, Kamboj M, et al. Laboratory Diagnosis of Central Nervous System Infection. Curr Infect Dis Rep. Nov 2016; 18(11): 35. PMID 27686677
2. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. Clin Microbiol Infect. Mar 2020; 26(3): 281-290. PMID 31760115
3. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens. J Clin Microbiol. Sep 2016; 54(9): 2251-61. PMID 27335149

4. Graf EH, Farquharson MV, Cárdenas AM. Comparative evaluation of the FilmArray meningitis/encephalitis molecular panel in a pediatric population. Diagn Microbiol Infect Dis. Jan 2017; 87(1): 92-94. PMID 27771208
5. Hanson KE, Slechta ES, Killpack JA, et al. Preclinical Assessment of a Fully Automated Multiplex PCR Panel for Detection of Central Nervous System Pathogens. J Clin Microbiol. Mar 2016; 54(3): 785-7. PMID 26719436
6. Gastrointestinal Tract Infections. https://www.uib.cat/depart/dba/microbiologia/ADSenfcomI/material_archivos/infeccion%20gastrointestinal.pdf. Accessed May 12, 2023.
7. Bintsis T. Foodborne pathogens. AIMS Microbiol. 2017; 3(3): 529-563. PMID 31294175
8. Sattar SBA, Singh S. Bacterial Gastroenteritis. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2019 Jan. https://www.ncbi.nlm.nih.gov/books/NBK513295/. Accessed May 12, 2023.
9. Burden of Norovirus Illness in the U.S. Centers for Disease Control and Prevention. https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html. Last reviewed March 5, 2021. Accessed May 12, 2023.
10. Centers for Medicare & Medicaid Coverage. Local Coverage Determination (LCD): Foodborne Gastrointestinal Panels Identified by Multiplex Nucleic Acid Amplification (NAATs) (L37709). CMS.gov. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37709&ver=20&bc=0. Revised April 17, 2022. Accessed May 11, 2023.
11. Beckmann C, Heininger U, Marti H, et al. Gastrointestinal pathogens detected by multiplex nucleic acid amplification testing in stools of pediatric patients and patients returning from the tropics. Infection. Dec 2014; 42(6): 961-70. PMID 25015433
12. Borst A, Box AT, Fluit AC. False-positive results and contamination in nucleic acid amplification assays: suggestions for a prevent and destroy strategy. Eur J Clin Microbiol Infect Dis. Apr 2004; 23(4): 289-99. PMID 15015033
13. Evaluation of automatic class III designation (de novo) for xTAG gastrointestinal pathogen panel (GPP) decision summary. Food and Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/reviews/K121454.pdf. Accessed May 11, 2023.
14. Claas EC, Burnham CA, Mazzulli T, et al. Performance of the xTAG® gastrointestinal pathogen panel, a multiplex molecular assay for simultaneous detection of bacterial, viral, and parasitic causes of infectious gastroenteritis. J Microbiol Biotechnol. 2013; 23(7): 1041-5. PMID 23711521
15. Khare R, Espy MJ, Cebelinski E, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. J Clin Microbiol. Oct 2014; 52(10): 3667-73. PMID 25100818
16. Buchan BW, Olson WJ, Pezewski M, et al. Clinical evaluation of a real-time PCR assay for identification of Salmonella, Shigella, Campylobacter (Campylobacter jejuni and C. coli), and shiga toxin-producing Escherichia coli isolates in stool specimens. J Clin Microbiol. Dec 2013; 51(12): 4001-7. PMID 24048539
17. Al-Talib H, Latif B, Mohd-Zain Z. Pentaplex PCR assay for detection of hemorrhagic bacteria from stool samples. J Clin Microbiol. Sep 2014; 52(9): 3244-9. PMID 24958797
18. Jiang Y, Fang L, Shi X, et al. Simultaneous detection of five enteric viruses associated with gastroenteritis by use of a PCR assay: a single real-time multiplex reaction and its clinical application. J Clin Microbiol. Apr 2014; 52(4): 1266-8. PMID 24478418
19. Freeman K, Mistry H, Tsertsvadze A, et al. Multiplex tests to identify gastrointestinal bacteria, viruses and parasites in people with suspected infectious gastroenteritis: a systematic review and economic analysis. Health Technol Assess. Apr 2017; 21(23): 1-188. PMID 28619124
20. Kosai K, Suzuki H, Tamai K, et al. Multicenter evaluation of Verigene Enteric Pathogens Nucleic Acid Test for detection of gastrointestinal pathogens. Sci Rep. Feb 04 2021; 11(1): 3033. PMID 33542335
21. Meltzer AC, Newton S, Lange J, et al. A randomized control trial of a multiplex gastrointestinal PCR panel versus usual testing to assess antibiotics use for patients with infectious diarrhea

in the emergency department. J Am Coll Emerg Physicians Open. Feb 2022; 3(1): e12616. PMID 35072157
22. Cybulski RJ, Bateman AC, Bourassa L, et al. Clinical Impact of a Multiplex Gastrointestinal Polymerase Chain Reaction Panel in Patients With Acute Gastroenteritis. Clin Infect Dis. Nov 13 2018; 67(11): 1688-1696. PMID 29697761
23. Beal SG, Tremblay EE, Toffel S, et al. A Gastrointestinal PCR Panel Improves Clinical Management and Lowers Health Care Costs. J Clin Microbiol. Jan 2018; 56(1). PMID 29093106
24. Darie AM, Khanna N, Jahn K, et al. Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial. Lancet Respir Med. Sep 2022; 10(9): 877-887. PMID 35617987
25. Clark TW, Lindsley K, Wigmosta TB, et al. Rapid multiplex PCR for respiratory viruses reduces time to result and improves clinical care: Results of a systematic review and meta-analysis. J Infect. May 2023; 86(5): 462-475. PMID 36906153
26. Huang HS, Tsai CL, Chang J, et al. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. Clin Microbiol Infect. Oct 2018; 24(10): 1055-1063. PMID 29208560
27. Mansuy JM, Mengelle C, Da Silva I, et al. Performance of a rapid molecular multiplex assay for the detection of influenza and picornaviruses. Scand J Infect Dis. Dec 2012; 44(12): 963-8. PMID 22830610
28. Dabisch-Ruthe M, Vollmer T, Adams O, et al. Comparison of three multiplex PCR assays for the detection of respiratory viral infections: evaluation of xTAG respiratory virus panel fast assay, RespiFinder 19 assay and RespiFinder SMART 22 assay. BMC Infect Dis. Jul 24 2012; 12: 163. PMID 22828244
29. Pierce VM, Hodinka RL. Comparison of the GenMark Diagnostics eSensor respiratory viral panel to real-time PCR for detection of respiratory viruses in children. J Clin Microbiol. Nov 2012; 50(11): 3458-65. PMID 22875893
30. Andrews D, Chetty Y, Cooper BS, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. BMC Infect Dis. Oct 10 2017; 17(1): 671. PMID 29017451
31. Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med. May 2017; 5(5): 401-411. PMID 28392237
32. Cytomegalovirus (CMV) and Congenital CMV Infection: Laboratory Testing. Centers for Disease Control and Prevention. https://www.cdc.gov/cmv/clinical/lab-tests.html. Page last reviewed April 28, 2020. Accessed May 12, 2023.
33. Mycoplasma pneumoniae Infections: Diagnostic Methods. Center for Disease Control and Prevention. https://www.cdc.gov/pneumonia/atypical/mycoplasma/hcp/diagnostic-methods.html. Last Reviewed June 5, 2020. Accessed May 12, 2023.
34. Zika Virus: Testing Guidance. Center for Disease Control and Prevention. https://www.cdc.gov/zika/hc-providers/testing-guidance.html. Last Reviewed December 9, 2019. Accessed May 12, 2023.
35. MacCannell T, Umscheil CA, Agarwal RK, et al. Guideline for the Prevention and Control of Norovirus Gastroenteritis Outbreaks in Healthcare Settings. CDC. Updated February 15, 2017. https://www.cdc.gov/infectioncontrol/pdf/guidelines/norovirus-guidelines.pdf. Accessed May 12, 2023.
36. Hall AJ, Vinje J, Lopman B, et al. Updated Norovirus Outbreak Management and Disease Prevention Guidelines. CDC MMWR. Published March 4, 2011. https://www.cdc.gov/mmwr/pdf/rr/rr6003.pdf. Accessed May 12, 2023.
37. Workowski KA, Bolan GA, Workowski KA, et al. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. Jun 05 2015; 64(RR-03): 1-137. PMID 26042815

38. Sexually Transmitted Infections Treatment Guidelines, 2021. Center for Disease Control and Prevention. https://www.cdc.gov/std/treatment-guidelines/default.htm. Last Reviewed July 22, 2021. Accessed May 12, 2023.
39. Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae 2014. CDC MMWR. Published March 14, 2014. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm. Accessed May 12, 2023.
40. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. CDC MMWR. Published January 16, 2009. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm?s_cid=mm5801a3_e. Accessed May 12, 2023.
41. NIH Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Updated April 12, 2022. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed on May 12, 2023.
42. Miller JM, Binnicker MJ, Campbell S, et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. Aug 31 2018; 67(6): e1-e94. PMID 29955859
43. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. Mar 15 2017; 64(6): e34-e65. PMID 28203777
44. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. Aug 01 2008; 47(3): 303-27. PMID 18582201
45. Lee DH, Vielemeyer O. Analysis of overall level of evidence behind Infectious Diseases Society of America practice guidelines. Arch Intern Med. Jan 10 2011; 171(1): 18-22. PMID 21220656
46. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. Mar 19 2018; 66(7): e1-e48. PMID 29462280
47. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. Nov 29 2017; 65(12): e45-e80. PMID 29053792
48. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. Feb 15 2016; 62(4): e1-50. PMID 26679628
49. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19. Published May 6, 2020. Updated December 23, 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/. Accessed on May 12, 2023.
50. Nellore A, Huprikar S. Vancomycin-resistant Enterococcus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. Sep 2019; 33(9): e13549. PMID 30913322
51. Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book: 2021 Report on the Committee on Infectious Diseases, 32nd Edition. American Academy of Pediatrics: 2021.
52. Puopolo KM, Lynfield R, Cummings JJ, et al. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics. Aug 2019; 144(2). PMID 31285392
53. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. May 2016; 111(5): 602-22. PMID 27068718
54. Filkins L, Hauser J, Robinson-Dunn B, Tibbetts R, Boyanton B, Revell P. Guidelines for the Detection and Identification of Group B Streptococcus. American Society for Microbiology. Published March 10, 2020. Updated July 23, 2021. https://asm.org/Guideline/Guidelines-for-the-Detection-and-Identification-of. Accessed May 12, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical condition/diagnosis
  - Microorganism in question
  - Past and present testing
  - Specific test being requested
- Pertinent laboratory and imaging 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
	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))
	0109U	Infectious disease (Aspergillus species), real-time PCR for detection of DNA from 4 species (A. fumigatus, A. terreus, A. niger, and A. flavus),

Type	Code	Description
		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 endotracheal aspirate, detection of 33 organismal and antibiotic resistance genes with limited semi-quantitative results
	0202U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
	0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (i.e., protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility
	0223U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
	0225U	Infectious disease (bacterial or viral respiratory tract infection) pathogen-specific DNA and RNA, 21 targets, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected
	0240U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected
	0241U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper

Type	Code	Description
		respiratory specimen, each pathogen reported as detected or not detected
	0301U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); ***(Code revision effective 1/1/2023)***
	0302U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); following liquid enhancement
	0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi
	0330U	Infectious agent detection by nucleic acid (DNA or RNA), vaginal pathogen panel, identification of 27 organisms, amplified probe technique, vaginal swab
	0351U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma-induced protein-10 (IP-10), and C-reactive protein, serum, algorithm reported as likelihood of bacterial infection ***(Code revision effective 1/1/2023)***
	0353U	Infectious agent detection by nucleic acid (DNA), Chlamydia trachomatis and Neisseria gonorrhoeae, multiplex amplified probe technique, urine, vaginal, pharyngeal, or rectal, each pathogen reported as detected or not detected ***(Code effective 10/1/2022)***
	0354U	Human papilloma virus (HPV), high-risk types (i.e., 16, 18, 31, 33, 45, 52 and 58) qualitative mRNA expression of E6/E7 by quantitative polymerase chain reaction (qPCR) ***(Code effective 10/1/2022)***
	0369U	Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique ***(Code effective 4/1/2023)***
	0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab ***(Code effective 7/1/2023)***
	0371U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogen, semiquantitative identification, DNA from 16 bacterial organisms and 1 fungal organism, multiplex amplified probe technique via quantitative polymerase chain reaction (qPCR), urine ***(Code effective 4/1/2023)***
	0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score ***(Code effective 4/1/2023)***
	0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen ***(Code effective 4/1/2023)***
	0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine ***(Code effective 4/1/2023)***

Type	Code	Description
	0402U	Infectious agent (sexually transmitted infection), Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium, multiplex amplified probe technique, vaginal, endocervical, or male urine, each pathogen reported as detected or not detected ***(Code effective 10/1/2023)***
	0416U	Infectious agent detection by nucleic acid (DNA), genitourinary pathogens, identification of 20 bacterial and fungal organisms, including identification of 20 associated antibiotic-resistance genes, if performed, multiplex amplified probe technique, urine ***(Code effective 10/1/2023)***
	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
	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
	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])
	87154	Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets
	87426	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; severe acute respiratory syndrome coronavirus (e.g., SARS-CoV, SARS-CoV-2 [COVID-19])
	87468	Infectious agent detection by nucleic acid (DNA or RNA); Anaplasma phagocytophilum, amplified probe technique ***(Code effective 1/1/2023)***
	87469	Infectious agent detection by nucleic acid (DNA or RNA); Babesia microti, amplified probe technique ***(Code effective 1/1/2023)***
	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
	87478	Infectious agent detection by nucleic acid (DNA or RNA); Borrelia miyamotoi, amplified probe technique ***(Code effective 1/1/2023)***
	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

Type	Code	Description
	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
	87484	Infectious agent detection by nucleic acid (DNA or RNA); Ehrlichia chaffeensis, amplified probe technique ***(Code effective 1/1/2023)***
	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
	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,

Type	Code	Description
		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
	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

Type	Code	Description
	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
	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)

Type	Code	Description
	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
	87635	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique
	87636	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) and influenza virus types A and B, multiplex amplified probe technique
	87637	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), influenza virus types A and B, and respiratory syncytial virus, multiplex amplified probe technique
	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
	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

Type	Code	Description
	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 review updated. Coding update.
01/01/2021	Coding update
06/01/2021	Coding update
10/01/2021	Annual Review. No change to policy statement. Policy guidelines and literature review updated.
02/01/2022	Coding update
08/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated. Coding update.
11/01/2022	Coding update
03/01/2023	Coding update
06/01/2023	Coding update
08/01/2023	Annual review. No change to policy statement. Policy guidelines and literature review updated.
11/01/2023	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.

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.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

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): 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 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	**Identification of Microorganisms Using Nucleic Acid Probes 2.04.10** **Policy Statement:** I. 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): A. Bartonella henselae or quintana B. Bordetella pertussis C. Candida species D. Chlamydia pneumoniae E. Chlamydia trachomatis F. Clostridium difficile G. Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB) H. Enterovirus I. Herpes simplex virus J. Human papillomavirus K. Influenza virus L. Legionella pneumophila M. Mumps N. Mycobacterium species O. Mycobacterium tuberculosis P. Mycobacterium avium-intracellulare Q. Mycoplasma pneumoniae R. Neisseria gonorrhoeae S. Rubeola (measles) T. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) U. Staphylococcus aureus V. Staphylococcus aureus, methicillin-resistant W. Streptococcus, group A X. Streptococcus, group B Y. Trichomonas vaginalis Z. Zika virus

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
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. Gardnerella 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	II. 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: A. Cytomegalovirus B. Hepatitis B virus C. Hepatitis C virus D. Human herpesvirus 6 E. Human Immunodeficiency Virus 1 (HIV-1) F. Human Immunodeficiency Virus 2 (HIV-2) III. 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. IV. The use of nucleic acid testing using a direct or amplified probe technique is considered **investigational** for the following microorganisms: A. Gardnerella vaginalis B. Hepatitis G V. The use of the following nucleic acid testing panel (*without* quantification of viral load) may be considered **medically necessary**: A. Respiratory virus panel VI. The use of the following nucleic acid testing panels (*with or without* quantification of viral load for viral panel elements) is considered **investigational**: A. Central nervous system pathogen panel B. Gastrointestinal pathogen panel