BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.10 Identification of Microorganisms Using Nucleic Acid Probes

Effective Policy Date: October 1, 2023

Original Policy Date: March 2012

Related Policies:

2.04.127 - Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

Identification of Microorganisms Using Nucleic Acid Probes

Description

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.

OBJECTIVE

The objective of this evidence review is to determine whether testing for microorganisms using nucleic acid probes improves the net health outcome in individuals with suspected infections.

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 the following microorganisms (see Policy Guidelines):

- Bartonella henselae or quintana
- Bordetella pertussis
- Candida species
- Chlamydia pneumoniae
- Chlamydia trachomatis
- Clostridium difficile
- Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
- Enterovirus
- Herpes simplex virus
- Human papillomavirus
- Influenza virus
- Legionella pneumophila
- Mumps
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium-intracellulare
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae
- Rubeola (measles)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Staphylococcus aureus
- Staphylococcus aureus, methicillin-resistant
- Streptococcus, group A
- Streptococcus, group B
- Trichomonas vaginalis
- Zika virus.

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 the following microorganisms:

- Cytomegalovirus
- Hepatitis B virus
- Hepatitis C virus

- HIV-1
- HIV-2
- Human herpesvirus 6.

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:

- Gardnerella vaginalis
- Hepatitis G.

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

- Respiratory virus panel.

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

- Central nervous system pathogen panel
- Gastrointestinal pathogen panel.

POLICY GUIDELINES

The use of molecular diagnostics for the diagnosis and management of *Borrelia burgdorferi* infection (Lyme disease) is addressed in evidence review 5.01.08.

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. Evidence review 2.04.127 (Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis) addresses the use of multitarget PCR tests for bacterial vaginosis.

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 (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.

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.

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).

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.

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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

Summary of Evidence

For individuals who have signs and/or symptoms of meningitis and/or encephalitis who receive a nucleic acid-based central nervous system (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 cerebrospinal fluid (CSF). The available central nervous system panel is highly specific for the included organisms, but the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest clinical validity study were false-positives. A negative panel result does not exclude infection due to pathogens not included in the panel. The evidence is insufficient to determine 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 gastrointestinal (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 randomized controlled trials (RCTs). Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. The systematic review reported that all 3 reviewed multiplex polymerase chain reaction systems were highly accurate. One RCT and 1 quasi-RCT evaluated utility of a respiratory panel and found benefits in time-to-treat and length of hospital stay. In addition, 1 subanalysis found fewer antibiotics being prescribed for patients diagnosed with the panel. The panel did not significantly affect duration of antibiotic use, readmission, or mortality rates. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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 2 provides an index of NAAT recommendation by virus/ infection.

Table 2. 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
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) have 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.[32,]

1.2 The CDC published diagnostic methods for mycoplasma pneumoniae.[33,] They cited NAAT as a method of diagnosis, along with culture or serology.

1.3 The CDC published updated guidelines on Zika virus testing.[34,]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.[35,36,] 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. [37,]These recommendations were most recently updated in 2021, with the publication of new guidelines and the following recommendations:[38,]

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 (eg., 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.[39,] 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.[40,] 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.[41,] The most recent update took place in 2023. 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.[42,] 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 3 describes the conditions for which IDSA recommends NAATs for diagnosing etiologic agents.

Table 3. 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.[43,] 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.[44,] 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."[45,])
- "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."[45,])
- "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*.[46,]

- "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.[47,] 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.[48,] 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.[49,] 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.[50,] 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.[51,] Their recommendations for appropriate diagnostic tests for the viruses and infections discussed in this policy are detailed in Table 4.

Table 4. 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
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 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).[52,] 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.[53,] 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.[54,] 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	New policy
December 2012	Replace policy	Policy updated with literature search, references updated, new information added to rationale for numerous probes. New medically necessary indication added for respiratory virus panel amplified probes.
December 2013	Replace policy	Policy updated with literature search. Candida species amplified probe changed from investigational to medically necessary. Medically necessary indication for Trichomonas vaginalis amplified probe added. References 8, 10, and 62-63 added.
December 2014	Replace policy	Policy updated with literature review. Added gastrointestinal pathogen panel as investigational to the policy statement. References 1, 27-28, 44-45 and 63-64 added
March 2018	Replace policy	Policy updated with literature review through October 16, 2017; references updated/added. Medically necessary statement added for non-quantified nucleic acid based testing for enterovirus, Legionella pneumophila, Mycoplasma pneumoniae, and Bartonella spp, and for quantified testing for human herpesvirus 6. Borrelia testing removed from policy. Investigational policy statement added for probes with quantification of viral load that do not meet criteria for quantification. Investigational statement added for central nervous system pathogen panel
March 2019	Replace policy	Policy updated with literature review through October 18, 2018; several references updated. Policy statements unchanged
June 2020	Replace policy	Policy updated with literature review through January 6, 2020; references added. Multiple major revisions made to the policy. Evidence review limited to central nervous system, gastrointestinal and respiratory pathogen panels. Detailed guidelines documented to support or not support NAAT testing indications for individual pathogens (bacteria and viruses). Policy statements changed: nuecleic acid testing using a direct or amplified probe technique is investigational for Gardnerella vaginalis. Nucleic acid testing panel (without quantification of viral load) is medically necessary for Respiratory virus panel. Bordetella pertussis, Chlamydia pneumoniae, Mumps, Rubelola, and Zika virus added to the medically necessary statement for nucleic acid testing using a direct or amplified probe technique (without quantification of viral load).
September 2020	Replace policy	Policy updated with literature review through May 27, 2020; references added. Guidelines added to support diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using NAAT. SARS-CoV-2 added to the first policy statement.
September 2021	Replace policy	Policy updated with literature review through May 3, 2021; references added and updated. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through May 10, 2022; references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through May 12, 2023; references added. Policy statements unchanged.