Identification of Microorganisms Using Nucleic Acid Probes

Policy # 00488
Original Effective Date: 10/21/2015
Current Effective Date: 10/12/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of nucleic acid testing using a direct or amplified probe technique (without quantification of viral load) to be **eligible for coverage**** for the following microorganisms:

- *Bartonella henselae* or *Quintana*
- *Bordetella pertussis*
- *Candida* species
- *Chlamydia pneumoniae*
- *Chlamydia trachomatis*
- *Clostridium difficile*
- *Enterococcus,* vancomycin-resistant (eg, enterococcus vanA, vanB)
- *Enterovirus*
- Herpes simplex virus
- Human papillomavirus
- Influenza virus
- *Legionella pneumophila*
- *Mycobacterium* species
- *Mycobacterium tuberculosis*
- *Mycobacterium avium intracellulare*
- *Mycoplasma pneumoniae*
- *Neisseria gonorrhoeae*
- *Rubeola (measles)*

- *Paramyxovirus (mumps)*
- *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for indications consistent with the Centers for Disease Control and Prevention (CDC) guidance related to COVID-19 testing*
- *Staphylococcus aureus*
- *Staphylococcus aureus*, methicillin resistant
- *Streptococcus,* group A
- *Streptococcus*, group B
- *Trichomonas vaginalis*
- *Zika virus*

Note: SARS-CoV2 testing required for work, school and recreational activities is excluded from coverage.

Based on review of available data, the Company may consider the use of nucleic acid testing using a direct or amplified probe technique (with or without quantification of viral load) to be **eligible for coverage**** for the following microorganisms:

- Cytomegalovirus
- Hepatitis B virus
- Hepatitis C virus
- HIV-1
- HIV-2
- Human herpesvirus 6

Based on review of available data, the Company may consider the use of the Respiratory Pathogen nucleic acid testing panel (without quantification of viral load) for patients with signs and symptoms of a respiratory infection when the result of testing is actionable and likely to guide treatment to be **eligible for coverage**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers the use of nucleic acid testing with quantification of viral load to be **investigational*** for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered to be eligible for coverage.**

Based on review of available data, the Company considers the use of nucleic acid testing using a direct or amplified probe technique to be **investigational*** for the following microorganisms:

- *Gardnernella vaginalis*
- *Hepatitis G virus*

Based on review of available data, the Company considers the use of the following nucleic acid testing panels (with or without quantification of viral load for viral panel elements) to be **investigational***:

- *Central nervous system pathogen panel*
- *Gastrointestinal pathogen panel*

Based on review of available data, the Company considers multitarget polymerase chain reaction testing for the diagnosis of bacterial vaginosis (including testing for Atopobium vaginae, Lactobacillus species, G. vaginalis, Megasphaera species, Mycoplasma hominis, Peptostreptococcus, Mobiluncus species, and other anaerobic gram-negative rods) to be **investigational***

Policy Guidelines

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

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 women, as likely to be caused by *C. albicans*. A presumptive diagnosis can be made in the clinical care setting. However, for complicated infections, the CDC states that NAATs may be necessary to test for multiple *Candida* subspecies. Complicated vulvovaginal candidiasis is classified as being recurrent or severe; or, in women with uncontrolled diabetes, debilitation, or immunosuppression, as less likely to be caused by a *C. albicans* species.

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.

Background/Overview

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.

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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 human immunodeficiency virus 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 (eg, HIV), fastidious or lengthy culture requirements (eg, *Mycobacteria, Chlamydia*, *Neisseria* species), or difficulty in collecting an appropriate sample (eg, 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA maintains a list of nucleic acid amplification tests (NAATs) that have been cleared by the Center for Devices and Radiological Health. 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 gastrointestinal panels when diagnosing gastroenteritis, and for respiratory panels.

Table 1. FDA Cleared NAATs for CNS, GI, 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 Gastrointestinal 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 Gastrointestinal Pathogen Panel	Applied Biocode (Santa Fe Springs, CA)	K190585	PCH
EntericBio Dx Assay	Serosep, Ltd (Annacotty, IE)	K182703	PCH
Filmarray Gastrointestinal 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)	K142033K140083	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

CDC: Centers for Disease Control and Prevention; CNS: central nervous system; DEN: de novo; GI: gastrointestinal; NAAT: nucleic acid amplification test; FDA: Food and Drug Administration.

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/Source

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.

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

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

For individuals who have signs and/or symptoms of respiratory infection who receive a nucleic acid-based respiratory pathogen panel, the evidence includes a systematic review and 2 randomized controlled trials (RCTs). Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. The systematic review reported that all 3 reviewed multiplex polymerase chain reaction systems were highly accurate. One RCT and 1 quasi-RCT evaluated utility of a respiratory panel and found benefits in

time-to-treat and length of hospital stay; in addition, 1 subanalysis found fewer antibiotics being prescribed for patients diagnosed with the panel. The panel did not significantly affect duration of antibiotic use, readmission, or mortality rates. The evidence is sufficient to determine the effects of the technology on health outcomes.

Bacterial vaginosis (BV) is a common medical condition resulting from an imbalance in the normal vaginal flora. Although the identification of Gardnerella vaginalis has traditionally been associated with BV, there is no single etiologic agent. Most cases are asymptomatic, and most symptomatic cases can be diagnosed using clinical and microscopic evaluation. Multitarget polymerase chain reaction (PCR) testing is proposed as an alternative to currently available laboratory tests to diagnose BV. This test may improve outcomes if it is a more accurate and reliable method to diagnose BV.

In individuals who have signs or symptoms of BV who receive multitarget PCR testing, the evidence includes several prospective studies on technical performance and diagnostic accuracy. The relevant outcomes are test validity, symptoms, and change in disease status. Several studies have evaluated the diagnostic accuracy of multitarget PCR tests for BV, including two studies evaluating commercially available tests. The studies found sensitivities between 90% and 95% and specificities between 85% and 97% compared with standard methods of diagnosis. Most studies used a combination of the Amsel criteria and Nugent scoring as the reference standard. There is a lack of direct evidence on the clinical utility of PCR testing for BV (ie, studies showing that testing leads to better patient management decisions and/or better health outcomes than current approaches). Moreover, a chain of evidence does not currently support multitarget testing because most symptomatic women can be diagnosed with a standard workup. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Numerous guidelines have been identified concerning the use of nucleic acid amplification tests (NAATs) for the diagnosis of the pathogens discussed in this review. Table 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	CDC (1.5.1)[b]	IDSA (3.1, 3.7), AAP (5.1)
CNS Pathogen Panel	IDSA (3.2, 3.3)	NA
Chlamydia pneumonia	CDC (1.5.3), IDSA (3.1[c])	AAP (5.1)
Chlamydia trachomatis	CDC (1.5.2,[c] 1.6[c]), IDSA (3.1), AAP (5.1)	NA
Clostridium difficile	NIH (2.1.2), AAP (5.1)	IDSA (3.1, 3.4)
Cytomagolovirus	CDC (1.1), NIH (2.1.3), IDSA (3.1,[c] 3.3)	AAP (5.1)
Enterovirus	IDSA (3.1), AAP (5.1)	NA
Gardnerella vaginalis	AAP (5.1)	CDC (1.5.4), IDSA (3.1)
GI Pathogen Panel	CDC (1.4[c]), IDSA (3.5), ACG (6.1)	NA
Hepatitis B	NIH (2.1.4), IDSA (3.1), AAP (5.1)	NA
Hepatitis C	CDC (1.5.5[c]), NIH (2.1.5), IDSA (3.1), AAP (5.1)	NA
Herpes Simplex Virus	CDC (1.5.6[c]), NIH (2.1.6), IDSA (3.1,[c] 3.3), AAP (5.1)	NA
Human Herpesvirus 6	IDSA (3.1,[c] 3.3)	AAP (5.1)
Human Papillomavirus	CDC (1.5.8[c]), AAP (5.1)	NA
HIV 1	CDC (1.5.7[c]), IDSA (3.1), AAP (5.1)	NA

Influenza virus	IDSA (3.1[c]), AAP (5.1)	NA
Legionella pneumophila	IDSA (3.1), AAP (5.1)	NA
Meningitis	NA	IDSA (3.6)
Mycobacteria Species	CDC (1.8), NIH (2.1.7), IDSA (3.1, 3.3)	AAP (5.1)
Mycoplasma pneumoniae	CDC (1.2[c]), IDSA (3.3), AAP (5.1)	NA
Neisseria gonorrhoeae	CDC (1.6[c]), IDSA (3.1), AAP (5.1)	NA
Respiratory Panel	None Identified	NA
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	IDSA (3.8)	NA
Staphylococcus aureus	IDSA (3.1), AAP (5.1)	NA
Streptococcus, Group A	IDSA (3.1)	AAP (5.1)
Streptococcus, Group B	CDC (1.7), AAP (5.2)	IDSA (3.1), AAP (5.1)
Trichomonas vaginalis	CDC (1.5.9), IDSA (3.1),[c] AAP (5.1)	NA
Vancomycin-resistant enterococcus	AST (4.1)	IDSA (3.1), AAP (5.1)
Zika	CDC (1.3), IDSA (3.1), AAP (5.1)	NA

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

[c] Indicates guidelines in which the issuing body specifically recommends that U.S. FDA-cleared NAATs be used.

A. Centers for Disease Control and Prevention

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

1.1 In 2019, the CDC published guidance for laboratory testing for Cytomagolovirus (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.

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

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

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

1.3 In 2017, the CDC updated its guidelines on norovirus gastroenteritis outbreak management and disease prevention. 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.

1.4 In 2015, the following recommendations were made for the use of NAATs in diagnosing sexually transmitted diseases.

1.5.1 For Candida Species:

- "PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis."

1.5.2 For Chlamydia and Gonorrhea:

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

1.5.3 For Chlamydia pneumoniae:

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

1.5.4 For Gardnerella vaginalis:

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

1.5.5 For Hepatitis C infection:

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

1.5.6 For Herpes Simplex Virus:

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

1.5.7 For HIV-1:

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

1.5.8 For Human Papillomavirus:

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

1.5.9 For Trichomonas vaginalis:

- NAAT is recommended for detecting *vaginalis* in women due to its high sensitivity and specificity. The APTIMA *T. vaginalis* assay (Hologic Gen-Probe, San Diego, CA) is FDA-cleared to detect *T. vaginalis* from vaginal, endocervical, or urine specimens for women.
- In 1 study, "[f]or *vaginalis* diagnosis in men, the sensitivity of self-collected penile-meatal swabs was higher than that of urine." However, there is currently no FDA-cleared test for men.

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

- NAATs are superior other available diagnostic tests in "overall sensitivity, specificity, and ease of specimen transport;"

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

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

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

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

B. National Institute of Health et al

2.1 In 2019, the NIH, CDC, and HIV Medicine Association of the IDSA published guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. 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 for diagnosing Bartonella infection. There are PCR "methods that have been developed for identification and speciation of Bartonella but are not widely available."

2.1.2 Clostridium difficile

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

2.1.3 Cytomegalovirus

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

2.1.4 Hepatitis B

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

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… is the preferred method for diagnosis of mucocutaneous HSV lesions caused by HSV."

2.1.7 Mycobacterium tuberculosis Infection and Disease

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

C. 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. NAATs were recommended diagnostic procedures for Enterovirus, Hepatitis C, Hepatitis B, Cytomegalovirus, Herpes Simplex Virus, Human Herpesvirus 6, HIV, Influenza Virus, and Zika Virus. NAATs were not recommended diagnostic procedures for Bacterial vaginosis. In addition to providing guidance on diagnosing these diseases, the guidelines also provided recommendations on testing for other conditions by testing for common etiologic agents. Table 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 Lacrimal and Eyelid Infections; Proctitis; Epididymitis and Orchitis; Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis
Clostridium difficile	Gastroenteritis, Infectious, and Toxin-Induced Diarrhea
Cytomegalovirus	Pericarditis and Myocarditis[a]; Encephalitis; Pneumonia in the Immunocompromised Host; Esophagitis; Gastroenteritis, Infectious, and Toxin-Induced Diarrhea; Burn Wound Infections[b]
Enterovirus	Meningitis; Encephalitis; Brochiolitis, Bronchitis, and Pertussis; Community-Acquired Pneumonia; Gastroenteritis, Infectious, and Toxin-Induced Diarrhea
Herpes Simplex Virus	Meningitis; Encephalitis; Immunocompromised Host; Esophagitis; Proctitis; Pathogens Associated with Cervicitis/Urethritis; Burn Wound Infection[b]; Periocular structure infections/ Conjunctivitis, Orbital and Periorbital Cellulitis, and Lacrimal and Eyelid Infections; Periocular Structure Infections/Keratitis; Pharyngitis; Genital Lesions
HIV	Pericarditis and Myocarditis; Meningitis[c]; Pharyngitis[c]
Human Herpesvirus 6	Encephalitis
Influenza	Encephalitis; Bronchiolitis, Bronchitis, and Pertussis; Community-Acquired Pneumonia; Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia; Pulmonary Infections in Cystic Fibrosis;
Legionella spp	Community-Acquired Pneumonia; Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia; Infections of the Pleural Space; Surgical Site Infections
Mycobacteria Species- both Tuberculosis and NTM	Community-Acquired Pneumonia; Infections of the Pleural Space; Osteomyelitis

Neisseria gonorrhoeae	Pharyngitis; Proctitis; Native Joint Infection and Bursitis; Epididymitis and Orchitis; Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis
Staphylococcus aureus	Burn Wound Infections for MRSA and S. aureus only, Trauma-Associated Cutaneous Infections; Surgical Site Infections
Streptococcus, Group A	Pharyngitis
Trichomonas vaginalis	Pathogens Associated with Cervicitis/Urethritis; Pathogens Associated with Pelvic Inflammatory Disease and Endometritis

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

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

3.2 In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis. 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. 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.")
- "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.")
- "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, HSV-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 Clostridium difficile.

- "The best-performing method (ie, 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. The following recommendations were made:

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

3.6 In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis. 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)."

3.7 In 2016, the IDSA published updated clinical practice guidelines for managing candidiasis. 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."

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

online format, as when substantive new information becomes available the recommendations will require frequent updating. The current recommendations (published May 6, 2020) support SARS-CoV-2 nucleic acid testing for the following groups:

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

The IDSA panel further recommends the following:

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

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

D. 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 infections in solid organ transplant patients. 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.

E. American Academy of Pediatrics

5.1 The current edition of the AAP Red Book describes the diagnostic and treatment options of many infectious diseases in the pediatric population. Their recommendations for appropriate diagnostic tests for the viruses and infections discussed in this policy are detailed in Table 4.

Table 4. Redbook Diagnostic Test Recommendations for the Pediatric Population

Infection	Diagnostic Test Recommendation
Bartonella henselae	IFA NAAT (PCR)
Candida Species	Clinical Evaluation Microscopy
Chlamydia pneumoniae	Serologic antigen test PCRs- "can provide a specific diagnosis but are not available in most clinical laboratories"
Chlamydia trachomatis	NAATs are recommended for C trachomatis urogenitial infections and in postpubescent individuals. They are not recommended for diagnosis C trachomatis conjunctivitis or pneumonia or in the evaluation of prepubescent children for possible sexual assault.
Clostridium difficile	Anaerobic cultures of wound exudate and blood should be performed.
Cytomegalovirus	Saliva PCR is the preferred diagnostic tool for screening.
Enterovirus	Reverse-transcriptase PCR and culture from a variety of specimens

Gardnerella vaginalis	Microscopy Numerous NAATs have been recommended when microscopy is unavailable
Hepatitis B	Serologic antigen tests NAATs
Hepatitis C	IgG antibody enzyme immunoassays NAATs
Herpes Simplex Virus	Cell culture NAATs- diagnostic method of choice for neonates with CNS infections, older children, and adults with HSE
Human Herpesvirus 6	Few developed assays are available commercially and do not differentiate between new, past, and reactivated infection. Therefore, these tests "have limited utility in clinical practice:" Serologic tests; PCR- the assays are not sensitive in younger children.
HIV 1	HIV DNA PCR- "preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18mo; HIV RNA PCR- "preferred test to identify non-B subtype HIV-1 infections… DNA PCR is generally preferred because of greater clinical experience with that assay."
Human Papillomavirus	"Detection of HPV infection is based on detection of viral nucleic acid or capsid protein."
Influenza Virus	"RT-PCR, viral culture tests, and rapid influenza molecular assays offer potential for high sensitivity as well as specificity and are recommended as the tests of choice."
Legionella pneumophila	BCYE Media Legionella antigen in urine Direct IFA Genus-specific PCR reaction-based assays

Meningitis	Cultures of blood and CSF NAATs- "useful in patients who receive antimicrobial therapy before cultures are obtained."
Mycobacteria Species	M tuberculosis disease: Chest radiography and physical examination While several NAATs are cleared by the FDA, "further research is needed before NAATs can be recommended routinely for the diagnosis of tuberculosis in children," Nontuberculous Mycobacteria: "definite diagnosis of NTM disease requires isolation of the organism."
Mycoplasma pneumonia	"PCR tests for M pneumoniae are available commercially and increasing replacing other tests, because PCR tests performed on respiratory tract specimens have sensitivity and specifically between 80% and 100%, yield positive results earlier in the course of illness than serologic tests, and are rapid."
Neisseria gonorrhoeae	"NAATs are far superior in overall performance compared with other N gonorrhoeae culture and nonculture diagnostic methods to test genital and nongenital specimens, but performance varies by NAAT type."
Staphylococcus aureus	"NAATS are approved for detection and identification of S aureus, including MRSA, in positive blood cultures."
Streptococcus, Group A	"Children with pharyngitis and obvious viral symptoms should not be tested or treated for GAS infection. Laboratory confirmation is required for cases in children without viral symptoms… culture on sheep blood agar can confirm GAS infection."
Streptococcus, Group B	"Gram-positive cocci in pairs or short chains by gram stain of body fluids that typically are sterile provide presumptive evidence of infection."

Trichomonas vaginalis	Microscopy NAATs are "the most sensitive mean of diagnosing T vaginalis infection and is encouraged for detection in females and males."
Vancomycin-resistant enterococcus	"Diagnosis is established by culture of usually sterile body fluids with appropriate biochemical testing and serologic analysis for definitive identification."
Zika	NAATs Trioplex real-time PCR assay Serologic testing

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

5.2 In 2019, the AAP published guidelines on managing infants at risk for GBS. 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."

F. 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. 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.

Centers for Disease Control and Prevention
The Centers for Disease Control and Prevention (2015) updated its guidelines on sexually transmitted diseases. Regarding the diagnosis of bacterial vaginosis (BV), the guidelines stated:

"BV can be diagnosed by....clinical criteria (i.e., Amsel's Diagnostic Criteria) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli … PCR [polymerase chain reaction] has been used in research settings for the detection of … organisms associated with BV, but evaluation of its clinical utility is still underway. Detection of specific organisms might be predictive of BV by PCR. Additional validation is needed...."

American College of Obstetricians and Gynecologists
Published in 2012 and reaffirmed in 2018, the American College of Obstetricians and Gynecologists has produced a Practice Bulletin on the prediction of preterm birth. The Bulletin stated that BV testing is not recommended as a screening strategy in asymptomatic pregnant women at increased risk of preterm birth.

U.S. Preventive Services Task Force Recommendations
The USPSTF (2008) recommendations on screening for BV in pregnancy have stated that:
"The USPSTF recommends against screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery." (Grade D recommendation) "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery." (I statement)
These recommendations are currently in revision. Draft recommendations for 2019 revision are available for public comment through November 4, 2019.The recommendation statements remain the same as the 2008 recommendations.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

During the Public Health Emergency for the COVID-19 pandemic, a number of Medicare exceptions and waivers have been implemented. For further information on testing, see the CMS website regarding Coronavirus Disease.

Ongoing and Unpublished Clinical Trials
Some currently ongoing trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03809117	A Randomized Controlled Trial of Biofire Film Array Gastrointestinal Panel Compared to Usual Care for Evaluation of Acute Infectious Diarrhea in the Emergency Department	176	Nov 2019
NCT03551340	Impact of the Introduction of Gasto-intestinal Panel by PCR on the Treatment of Patients with Gastroenteritis	210	Mar 2020
NCT03895281	Clinical Evaluation of the FilmArray®‡ Meningitis/Encephalitis (ME) Panel	150	Apr 2020
NCT03452826	Combined Use of a Respiratory Broad Panel MULTIplex PCR and Procalcitonin to Reduce Antibiotics Exposure in Patients With Severe Community-Acquired Pneumonia: a Multicentre, Parallel-group, Open-label, Randomized Controlled Trial (MULTI-CAP)	450	Aug 2020
NCT03362970	Improvements Through the Use of a Rapid Multiplex PCR Enteric Pathogen Detection Kit in Children With Hematochezia	60	Dec 2020

NCT03840603	PROARRAY: Impact on PCT+ FilmArray RP2 Plus Use in LRTI Suspicion in Emergency Department	444	Jan 2021
NCT04372004	Comparison of the Efficacy of Rapid Tests to Identify COVID-19 Infection (CATCh COVID-19) (CATCH COVID-19)	100	June 2021

NCT: national clinical trial.

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Policy History

Original Effective Date: 10/21/2015
Current Effective Date: 10/12/2020
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. New Policy.
02/04/2016 Medical Policy Committee review

02/17/2016 Medical Policy Implementation Committee approval. Reorganized policy statements and added new pathogens to coverage statements (enterovirus, *Legionella pneumophila*, *Mycoplasma pneumoniae, hominus and genitalium* and *Bartonella, Megasphaera,* BVAB2 and *Atopobium vaginae. and for quantified testing for human herpesvirus 6).. Borrelia testing removed from policy.*

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update

02/02/2017 Medical Policy Committee review

02/15/2017 Medical Policy Implementation Committee approval. No change to coverage.

02/01/2018 Medical Policy Committee review

02/21/2018 Medical Policy Implementation Committee approval. Coverage statement revised to track BCBSA.

02/07/2019 Medical Policy Committee review

02/20/2019 Medical Policy Implementation Committee approval. No change to coverage.

04/02/2020 Medical Policy Committee review

04/08/2020 Medical Policy Implementation Committee approval. 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 accordingly and edited for clarity.
Added investigational statement, "Based on review of available data, the Company considers multitarget polymerase chain reaction testing for the diagnosis of bacterial vaginosis to be investigational."

09/03/2020 Medical Policy Committee review

09/09/2020 Medical Policy Implementation Committee approval. SARS-CoV-2 added to the eligible for coverage statement. Policy guidelines updated. Added statement saying Respiratory pathogen panel is eligible for coverage for patients with signs and symptoms of a respiratory infection when the result of testing is actionable and likely to guide treatment.

12/11/2020 Coding update

Next Scheduled Review Date: 09/2021

Identification of Microorganisms Using Nucleic Acid Probes

Policy # 00488
Original Effective Date: 10/21/2015
Current Effective Date: 10/12/2020

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0097U, 0140U, 0141U, 0142U, 0151U, 0152U, 87472, 87482, 87483, 87487, 87492, 87503, 87505, 87506, 87507, 87510, 87511, 87512, 87525, 87526, 87527, 87530, 87542, 87552, 87557, 87562, 87582, 87592, 87652, 87797, 87798, 87799 Codes added eff 1/1/2021: 81513, 81514
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally

recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.
‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.