



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Identification of Microorganisms Using Nucleic Acid Probes

Policy #: 548

Latest Review Date: March 2022

Category: Medicine

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after April 1, 2020:

For respiratory viral panels, see LCD L37713/ Article A56851.

For gastrointestinal viral panels, see LCD L37709/Article 56593.

Blue Advantage will treat the **use of nucleic acid testing using a direct or amplified probe technique** (without quantification of viral load) as a **covered benefit** for the following microorganisms (see Table 1 at the end of this section for details on coding):

- Bartonella henselae or quintana
- Candida species
- Chlamydia pneumoniae
- Chlamydia trachomatis
- Clostridium difficile
- Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
- Enterovirus
- Gardnerella vaginalis
- Herpes simplex virus
- Human papillomavirus (high-risk type)
- Legionella pneumophila
- Legionella pneumophila
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae
- 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

Blue Advantage will treat the **use of nucleic acid testing using a direct or amplified probe technique** (with or without quantification of viral load) as a **covered benefit** for the following microorganisms:

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

- Influenza virus

Blue Advantage will treat the **use of nucleic acid testing using a direct or amplified probe technique with or without quantification of viral load for microorganisms that are not included in the above list of microorganisms** as a **non-covered benefit and investigational**, including, but not limited to:

- Hepatitis G virus
- Human papillomavirus (low risk type)

Blue Advantage will treat the **use of nucleic acid testing expanded panels using a direct or amplified probe technique (with or without quantification of viral load)** as a **non-covered benefit and investigational** for the following microorganisms including but not limited to:

- Bacterial Vaginosis (BV) panel
- Infectious Disease (fungus and/or bacteria) Panel
- Genitourinary Pathogen Panel

Blue Advantage will treat **multitarget polymerase chain reaction testing for the diagnosis of bacterial vaginosis** as a **non-covered benefit** and as **investigational**.

CURRENT CODING:

CPT CODES:

The table below provides a list of CPT codes for various nucleic acid probes.

Table. CPT Codes for Nucleic Acid Probes

Pathogen	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or quintan ^a		87471 (Med Nec)	87472 (Inv) 0301U, 0302U (eff 1/1/22) (Inv—ddPCR)
Bacterial vaginosis			81513-81514 (Inv) (eff 1/1/21)
Blood stream pathogen identification		87154 (eff 1/1/22) (Med Nec)	
Borrelia borgdorferi ^a	87475 (Med Nec)	87476 (Med Nec)	

		87481 (Med Nec)	
Candida species ^b	87480 (Med Nec)	0068U (eff 10/01/18) (Med Nec)	87482 (Inv)
Central Nervous System Pathogen Panel		87483 (eff 01/01/17) (Med Nec)	
Chlamydia pneumoniae	87485 (Med Nec)	87486 (Med Nec)	87487 (Inv)
Chlamydia trachomatis	87490 (Med Nec)	87491 (Med Nec)	87492 (Inv)
Clostridium difficile	87493 (Med Nec)		
Cytomegalovirus	87495 (Med Nec)	87496 (Med Nec)	87497 (Med Nec)
Enterococcus, Vancomycin resistant (e.g., enterococcus van A, van B)		87500 (Med Nec)	
Enterovirus		87498 (Med Nec)	
Gardnerella vaginalis	87510 (Med Nec)	87511 (Med Nec)	87512 (Inv)
Genitourinary Pathogen Panel		0321U (Inv) (eff 4/1/22)	
Hepatitis B		87516 (Med Nec)	87517 (Med Nec)
Hepatitis C	87520 (Med Nec)	87521 (Med Nec)	87522 (Med Nec)
Hepatitis G	87525 (Inv)	87526 (Inv)	87527 (Inv)
Herpes simplex virus	87528 (Med Nec)	87529 (Med Nec)	87530 (Inv)

Human Herpes virus-6	87531 (Med Nec)	87532 (Med Nec)	87533 (Med Nec)
Human Immunodeficiency Virus 1 (HIV-1)	87534 (Med Nec)	87535 (Med Nec)	87536 (Med Nec)
Human Immunodeficiency Virus 2 (HIV-2)	87537 (Med Nec)	87538 (Med Nec)	87539 (Med Nec)
Human Papillomavirus (HPV)		87623(Inv) (<i>low- risk type</i>) 87624-87625 (Med Nec) (<i>high- risk type</i>)	
Infectious Agent detection and identification			0112U (eff 10/01/19) (Inv)
Infectious disease		0140U-0142U (eff 01/01/20) (Inv)	81513-81514 (eff 1/1/21) (Inv)
Influenza virus	87501 (Med Nec)	87502 (Med Nec)	87503 (Med Nec)
Legionella pneumophila	87540 (Med Nec)	87541 (Med Nec)	87542 (Inv)
Mycobacterium species	87550 (Med Nec)	87551(Med Nec)	87552 (Inv)
Mycobacterium tuberculosis	87555 (Med Nec)	87556 (Med Nec)	87557 (Inv)
Mycobacterium avium intracellulare	87560 (Med Nec)	87561 (Med Nec)	87562 (Inv)
Mycoplasma pneumoniae	87580 (Med Nec)	87581 (Med Nec)	87582 (Inv)

Neisseria gonorrhoeae	87590 (Med Nec)	87591 (Med Nec)	87592 (Inv)
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ^c		87635 (eff 3/13/20) (Med Nec)	
Staphylococcus aureus		87640 (Med Nec)	
Staphylococcus aureus, methicillin resistant		87641 (Med Nec)	
Streptococcus group A ^d	87650 (Med Nec)	87651 (Med Nec)	87652 (Inv)
Streptococcus group B ^e		87653 (Med Nec)	
Trichomonas vaginalis	87660 (Med Nec)	87661 (Med Nec)	
Unlisted (infectious agent detection by nucleic acid (DNA or RNA, not otherwise specified) ^f	87797 (Inv)	87798 (Inv)	87799 (Inv)
Zika Virus		87662 (Med Nec)	

^a Refer to medical policy #359, Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease.

^b For uncomplicated infections, testing for only one candida species, C albicans, may be considered medically necessary. For complicated infections, testing for multiple candida subspecies may be considered medically necessary. The Centers for Disease Control and Prevention classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent or mild to moderate or likely to be C. albicans or in non-immunocompromised women.

Complicated vulvovaginal candidiasis is classified as being recurrent or severe or not a C. albicans species or in women with uncontrolled diabetes, debilitation or immunosuppression.

^c 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).

^d Antibiotic sensitivity of streptococcus A cultures is frequently 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.

^e In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared to 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.

^f Testing submitted with these codes will be handled on a case by case basis. A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy.

Table Key:

Med Nec—meets medical criteria for coverage

Inv—does not meet medical criteria for coverage

Eff—effective

Effective for dates of service January 15, 2020, through March 31, 2020:

For respiratory viral panels, see LCD L37713/Article A56851.

For gastrointestinal viral panels, see LCD L37709/Article 56593.

Blue Advantage will treat the use of **nucleic acid testing** using a direct or amplified probe technique (without quantification of viral load) as a **covered benefit** for the following microorganisms (see Table 1 at the end of this section for details on coding):

- Bartonella henselae or quintana
- Candida species
- Chlamydia trachomatis
- Clostridium difficile
- Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
- Enterovirus
- Gardnerella vaginalis
- Herpes simplex virus
- Human papillomavirus
- Legionella pneumophila
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae
- Staphylococcus aureus
- Staphylococcus aureus, methicillin resistant
- Streptococcus, group A
- Streptococcus, group B
- Trichomonas vaginalis

Blue Advantage will treat **the use of nucleic acid testing** using a direct or amplified probe technique (with or without quantification of viral load) as a **covered benefit** for the following microorganisms:

- Cytomegalovirus
- Hepatitis B virus
- Hepatitis C virus
- HIV-1

- HIV-2
- Human herpes virus 6
- Influenza virus

Blue Advantage will treat **the use of nucleic acid testing** with quantification of viral load for microorganisms that are not included in the list of microorganisms as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat the **use of nucleic acid testing using a direct or amplified probe technique** (with or without quantification of viral load) as a **non-covered benefit** and as **investigational** for the following microorganisms including but not limited to:

- Chlamydomphila pneumoniae
- Hepatitis G virus
- Human papillomavirus (low risk panel)

CPT codes **87797**, **87798**, and **87799** describe the use of direct probe, amplified probe, and quantification, respectively, for infectious agents not otherwise specified. Testing submitted with these codes will be handled on a case-by-case basis. A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy. Table 1 provides a list of CPT codes for various nucleic acid probes.

A new PLA code is **effective 10/01/18** that represents the MYCODART Dual Amplification Real Time PCR Panel: **0068U** Candida species panel (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. kruseii*, *C. tropicalis*, and *C. auris*), amplified probe technique with qualitative report of the presence or absence of each species.

A new PLA code is **effective 10/01/19** that represents MicroGenDX: **0112U** - Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug resistance gene. (**Inv**)

Table. CPT Codes for Nucleic Acid Probes

Pathogen	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or quintana		87471 (Med Nec)	87472 (Inv)
Borrelia burgdorferi ^a	87475 (Med Nec)	87476 (Med Nec)	
Candida species ^b	87480 (Med Nec)	87481 (Med Nec)	87482 (Inv)
Chlamydia pneumoniae	87485 (Inv)	87486 (Inv)	87487 (Inv)

Chlamydia trachomatis	87490 (Med Nec)	87491 (Med Nec)	87492 (Inv)
Clostridium difficile	87493 (Med Nec)		
Cytomegalovirus	87495 (Med Nec)	87496 (Med Nec)	87497 (Med Nec)
Enterococcus, Vancomycin resistant (e.g., enterococcus van A, van B)		87500 (Med Nec)	
Enterovirus		87498 (Med Nec)	
Gardnerella vaginalis	87510 (Med Nec)	87511 (Med Nec)	87512 (Inv)
Central Nervous System Pathogen Panel		87483 (eff 01/01/17) (Med Nec)	
Hepatitis B		87516 (Med Nec)	87517 (Med Nec)
Hepatitis C	87520 (Med Nec)	87521 (Med Nec)	87522 (Med Nec)
Hepatitis G	87525 (Inv)	87526 (Inv)	87527 (Inv)
Herpes simplex virus	87528 (Med Nec)	87529 (Med Nec)	87530 (Inv)
Human Herpes virus-6	87531 (Med Nec)	87532 (Med Nec)	87533 (Med Nec)
Human Immunodeficiency Virus 1 (HIV-1)	87534 (Med Nec)	87535 (Med Nec)	87536 (Med Nec)
Human Immunodeficiency Virus 2 (HIV-2)	87537 (Med Nec)	87538 (Med Nec)	87539 (Med Nec)
Human Papillomavirus (HPV)		87623(Inv) 87624-87625 (Med Nec)	
Influenza virus	87501 (Med Nec)	87502 (Med Nec)	87503 (Med Nec)

Legionella pneumophila	87540 (Med Nec)	87541 (Med Nec)	87542 (Inv)
Mycobacterium species	87550 (Med Nec)	87551(Med Nec)	87552 (Inv)
Mycobacterium tuberculosis	87555 (Med Nec)	87556 (Med Nec)	87557 (Inv)
Mycobacterium avium intracellulare	87560 (Med Nec)	87561 (Med Nec)	87562 (Inv)
Mycoplasma pneumoniae	87580 (Med Nec)	87581 (Med Nec)	87582 (Inv)
Neisseria gonorrhoeae	87590 (Med Nec)	87591 (Med Nec)	87592 (Inv)
Staphylococcus aureus		87640 (Med Nec)	
Staphylococcus aureus, methicillin resistant		87641 (Med Nec)	
Streptococcus group A ^c	87650 (Med Nec)	87651 (Med Nec)	87652 (Inv)
Streptococcus group B ^d		87653 (Med Nec)	
Trichomonas vaginalis	87660 (Med Nec)	87661 (Med Nec)	

^a Refer to medical policy #359, Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease.

^b For uncomplicated infections, testing for only one candida species, C albicans, may be considered medically necessary. For complicated infections, testing for multiple candida subspecies may be considered medically necessary. The Centers for Disease Control and Prevention classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent or mild to moderate or likely to be C. albicans or in non-immunocompromised women.

Complicated vulvovaginal candidiasis is classified as being recurrent or severe or not a C. albicans species or in women with uncontrolled diabetes, debilitation or immunosuppression.

^c Antibiotic sensitivity of streptococcus A cultures is frequently 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.

^d In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared to 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.

Table Key:

Med Nec—meets medical criteria for coverage

Inv—does not meet medical criteria for coverage

Eff—effective

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

Nucleic Acid Probes

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

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

The direct probe technique, amplified probe technique, and probe with quantification methods vary based on the degree to which the nucleic acid is amplified and the method for measurement of the signal. The direct probe technique refers to detection methods in which nucleic acids are detected without an initial amplification step. The amplified probe technique refers to detection

methods in which either target, probe, or signal amplification is used to improve the sensitivity of the assay over direct probe techniques, without quantification of nucleic acid amounts.

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

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

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

Classically, identification of microorganisms relies either on the culture of body fluids or tissues or identification of antigens, using a variety of techniques including direct fluorescent antibody technique and qualitative or quantitative immunoassays. These techniques are problematic when the microorganism exists in very small numbers or is technically difficult to culture. Indirect identification of microorganisms by immunoassays for specific antibodies reactive with the microorganism is limited by difficulties in distinguishing between past exposure and current infection.

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

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

response to treatment. These include cases where quantification of viral load provides prognostic information or is used to measure response to therapy.

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

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

Bacterial Vaginosis

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.

BV is a condition caused by an imbalance in the normal bacteria vaginal flora. It is common, especially in women of reproductive age. While there is no single known etiologic agent, there is a shift in vaginal flora that involves depletion of hydrogen peroxide-producing *Lactobacillus* species with a rise in vaginal pH and overgrowth of other bacteria, including *Gardnerella vaginalis*, *Mycoplasma hominis*, *Peptostreptococcus*, *Mobiluncus* species, and other anaerobic gram-negative rods.

Vaginal culture is not an appropriate diagnostic method to identify BV because BV is not caused by the presence of a particular bacterial species.

Various commercial tests provide rapid and accurate pH evaluation and amine detection. For example, automated devices that measure the volatile gases produced from vaginal samples and a colorimetric pH test are commercially available.

Nucleic acid probes of DNA fragments are available to detect and quantify specific bacteria in vaginal fluid samples. Polymerase chain reaction (PCR) methods extract and amplify the DNA fragments using either universal or specific primers. The result can be qualitative (to assess whether a specific microorganism is present) or quantitative (to assess how many microorganisms are present). The technology can be used to measure multiple organisms (e.g., those known to be associated with BV) at the same time and is commercially available as multitarget PCR testing.

Proposed Multitarget PCR Tests

The SureSwab Total (Quest Diagnostics) test involves obtaining vaginal swab specimens, extracting total DNA, and quantitating the four types of bacteria using PCR. Results are reported as log cells per milliliter for each organism and concentrations of all Lactobacilli species are reported together then classified into one of the following three categories: not supportive, equivocal, and supportive.

A classification of not supportive of BV diagnosis is based on:

- The presence of Lactobacillus species, *G. vaginalis* levels <6.0 log cells/mL, and absence of *Atopobium vaginae* and *Megasphaera* species; or
- The absence of Lactobacillus species, *G. vaginalis* levels <6.0 log cells/mL, and absence of *A. vaginae* and *Megasphaera* species; or
- The absence of all targeted organisms.

A classification of equivocal is based on:

- The presence of Lactobacillus species, plus *G. vaginalis* at least 6.0 log cells/mL, and/or presence of *A. vaginae* and/or *Megasphaera* species.

A classification of supportive of BV diagnosis is based on the absence of Lactobacillus species, and presence of *G. vaginalis* levels of at least 6.0 log cells/mL, and presence of *A. vaginae* and/or *Megasphaera* species.

Another product, the BD Max (Becton, Dickinson), tests for markers of BV and vaginitis. The test uses a similar process to that described for SureSwab. Vaginal swab specimens are collected, DNA is extracted, and real-time PCR is used to quantitate targeted organisms. Results of BV marker tests are not reported for individual organisms. Instead, qualitative BV results are reported as positive or negative for BV based on the relative quantity of the various organisms. The Aptima BV Assay was cleared by the FDA with the BD Max as the predicate device. The Aptima assay is a nucleic acid amplification test (NAAT) for detection and quantitation of ribosomal RNA.

Medical Diagnostics Laboratory offers a Bacterial Vaginosis Panel. Markers are assessed using real-time PCR and Lactobacillus is profiled using quantitative PCR. GenPath Diagnostics also offers a bacterial vaginosis test.

The NuSwab® Select BV test (Laboratory Corporation of America) uses semiquantitative PCR analysis of three predictive marker organisms of vaginal dysbiosis to generate a total score that is associated with the presence or absence of BV. In this test system, samples with a total score of zero to one are considered negative for BV, samples with a score of three to six are positive for BV, and samples with a score of two are indeterminate for BV.

Several of the manufacturers of the BV tests also have extensions that include other causes of vaginitis such as *Trichomonas vaginalis* and *Candidiasis* species.

KEY POINTS:

The most recent literature review was conducted for the period through November 18, 2021.

Summary of Evidence

For individuals who receive a nucleic acid-based gastrointestinal pathogen panel testing (GIPP), the evidence includes prospective and retrospective evaluations of the tests' sensitivity and specificity. Relevant outcomes include test accuracy and validity, other test performance measures, 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. The evidence is sufficient 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 two 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 three reviewed multiplex PCR systems were highly accurate. One RCT and one quasi-RCT evaluated utility of a respiratory panel and found benefits in time-to-treat and length of hospital stay; in addition, one sub analysis found fewer antibiotics being prescribed for patients diagnosed with the panel. However, 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.

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 five studies evaluating commercially available tests. The studies found sensitivities between 84% 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 (i.e., 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 that the technology results in an improvement in the net health outcomes.

For other nucleic acid probes discussed in this review, the tests' clinical utility was evaluated based on whether there is demonstrated clinical validity, along with either direct evidence of improved outcomes or a chain of evidence indicating that changes in management leading to improved outcomes are likely to occur with testing.

Practice Guidelines and Position Statements

Numerous guidelines have been identified concerning the use of NAATs for the diagnosis of the pathogens discussed in this review.

American Academy of Pediatrics

The 2018 edition of the American Academy of Pediatrics (AAP) Red Book describes the diagnostic and treatment options for many infectious diseases in the pediatric population.

American College of Gastroenterology

In 2016, the American College of Gastroenterology published clinical guidelines on the diagnosis, treatment, and prevention of acute diarrheal infections in adults. 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 College of Obstetricians and Gynecologists

Published in 2012 and reaffirmed in 2018, the American College of Obstetricians and Gynecologists (ACOG) 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.

Published in 2020, the ACOG has issued a Practice Bulletin on vaginitis in nonpregnant patients. The Bulletin made the following recommendations on the initial evaluation of patients with symptoms of vaginitis, citing CDC guidelines:

"A complete medical history, physical examination of the vulva and vagina, and clinical testing of vaginal discharge (i.e., pH testing, a potassium hydroxide "whiff test," and microscopy) are recommended for the initial evaluation of patients with vaginitis symptoms."

The Bulletin noted that single-swab multiplex PCR testing "may be a promising alternative to microscopy," but that its clinical utility is still under evaluation.

American Society for Microbiology

In 2020, the American Society for Microbiology updated the 2010 guidelines on detecting and identifying GBS that were originally published by the CDC. 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.

American Society of Transplantation

In 2019, The American Society of Transplantation Infectious Diseases Community of Practice published guidelines which addressed vancomycin-resistant enterococci infections in solid organ transplant patients. 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.

Centers for Disease Control and Prevention

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

- The CDC published guidance for laboratory testing for cytomegalovirus (CMV), the guideline stated that the standard laboratory test for congenital CMV is 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 person >12 months of age.
- The CDC published diagnostic methods for mycoplasma pneumoniae. They cited NAAT as a method of diagnosis, along with culture or serology.
- The CDC published updated guidelines on Zika virus testing. 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.
- 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.
- In 2015, the following recommendations were made for the use of NAATs in diagnosing sexually transmitted diseases:
 - For candida species: "PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis."
 - 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]) three to four weeks after treatment and then retested within three 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 < three weeks after completion of therapy is not recommended because the continued presence of nonviable organisms can lead to false-positive results."
- For chlamydia pneumoniae: NAAT is recommended as an alternative to tissue culture, which "is the definitive standard diagnostic test for chlamydial pneumonia...NAATs are not FDA-cleared for the detection of chlamydia from nasopharyngeal specimens, and clinical laboratories must verify the procedure according to CLIA regulations."
- For gardnerella vaginalis: Although PCR has been researched "for the detection of various organisms associated with BV [bacterial vaginosis]," its clinical utility has not yet been established.
- For hepatitis C infection:
 - NAATs are recommended for screening pregnant women with known risk factors; NAAT "is necessary to confirm the diagnosis of current HCV infection."
 - In addition, "testing for HCV infection should include use of an FDA-cleared test for antibody to HCV...followed by NAAT to detect HCV RNA for those with a positive antibody result."
- For herpes simplex virus:
 - "Cell culture and PCR are the preferred HSV tests for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions;" and
 - "PCR is the test of choice for diagnosing HSV infections affecting the central nervous system and systemic infections."
- For 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.
- 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;
 - The "use of non-oncogenic tests is not recommended;" and
 - "HPV assays should be FDA-cleared and used only for the appropriate indications" and should not be performed if the patient is "deciding whether to vaccinate against HPV;" while "conducting STD screening in

women or men at risk for STDs;” when “providing care to persons with genital warts or their partners;” when “conducting screening for cervical cancer as a stand-alone test;” when “testing women aged <30 years as part of routine cervical cancer screening;” or when “testing oral or anal specimens.”

- For *Trichomonas vaginalis*:
 - NAAT is recommended for detecting *T 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 one study, “[f]or *T vaginalis* diagnosis in men, the sensitivity of self-collected penile-meatal swabs was higher than that of urine.” However, there is currently no FDA-cleared test for men.
- In 2014, the CDC published recommendations regarding the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. It stated:
 - NAATs are superior other available diagnostic tests in “overall sensitivity, specificity, and ease of specimen transport;”
 - The use of “NAAT to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls” is supported by evidence; and
 - Only NAATs that have been cleared by the FDA for detection of *C. trachomatis* and *N. gonorrhoeae* should be used “as screening or diagnostic tests because they have been evaluated in patients with and without symptoms”.
- 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.”
- In 2009, the CDC published updated guidelines for the use of NAATs in the 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 one to two weeks to one to two days.”

In 2021, the Centers for Disease Control and Prevention updated its guidelines on sexually transmitted infections. Regarding the diagnosis of bacterial vaginosis (BV), the guidelines stated:

“BV can be diagnosed by....clinical criteria (i.e., Amsel’s Diagnostic Criteria) or by determining the Nugent score from a vaginal Gram stain. Vaginal Gram stain, considered the reference standard laboratory method for diagnosing BV, is used to determine the relative concentration of lactobacilli ...”

The guidelines state that multiplex PCR assays are available, but noted that traditional methods of BV diagnosis, including the Amsel criteria, Nugent score, and the Affirm VP III assay, remain useful for diagnosing symptomatic BV because of their lower cost and ability to provide a rapid diagnosis. The guidelines also stated that BV nucleic acid amplification tests should be used among symptomatic women only (e.g., women with vaginal discharge, odor, or itch) because their accuracy is not well defined for asymptomatic women.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE; 2008) updated its clinical guideline on antenatal care for uncomplicated pregnancies in 2019. Regarding the screening of asymptomatic bacterial vaginosis, the guidelines stated:

"Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk of preterm birth and other adverse reproductive outcomes."

National Institute of Health et al

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. In these guidelines, NAATs are discussed in the following situations:

- *Bartonella* species: For patients with suspected bacillary angiomatosis, serologic tests are the standard of care of diagnosing *Bartonella* infection. There are PCR “methods that have been developed for identification and speciation of *Bartonella* but they are not widely available.”
- *Clostridioides (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 four to six week, those who reside in a long-term care facility, those with CD4 counts <200 cells/mm³, those taking acid-suppressive medication, and those with moderate-to-severe community-acquired diarrhea.”

- Cytomegalovirus: For patients with suspected CMV disease, “viremia can be detected 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.”
- 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.
- Hepatitis C: Patients with HIV are recommended to undergo routine hepatitis C screening, initially “performed using the most sensitive immunoassays licensed for detection of antibody to HCV in blood.” The use of NAATs are not mentioned for initial testing in patients with HIV.
- Herpes Simplex Virus: “HSV DNA PCR and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV.”
- Mycobacterium tuberculosis infection and disease: “Rapid diagnosis is essential in patients with HIV given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB.”; “NAA tests have at least two uses among patients with suspected HIV-related TB. First, NAA assays, if positive, are highly predictive of TB disease when performed on AFB smear-positive specimens.... Second, NAA tests are more sensitive than AFB smear, being positive in 50% to 80% of smear-negative, culture- positive specimens and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen.”

Infectious Disease Society of America et al

The IDSA has partnered with various societies to publish nine recommendations regarding the use of NAATs to diagnose the viruses and infections discussed.

In 2018, the IDSA and the American Society for Microbiology published a guide on the diagnosis of infectious diseases. 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.

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

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.)

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, herpes simplex virus 1 and 2, Human herpesvirus 6, Bartonella henselae, Mycoplasma pneumoniae, and Mycobacterium tuberculosis.

In 2018, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published weak recommendations with low quality evidence for the use of NAATs to diagnose Clostridioides (Clostridium) difficile.

- “The best-performing method (i.e., in use positive and negative predictive value) for detecting patients at increased risk for clinically significant C. difficile [CDI] infection” is use of a “stool toxin test as part of a multistep algorithm...rather than NAAT along for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission.”
- “The most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms” is use of “a NAAT alone or a multistep algorithm for testing...rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission.”

In 2017, the IDSA published clinical practice guidelines for the diagnosis and management of infectious diarrhea. 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 >two 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).

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.”

In 2020, the IDSA established a panel composed of eight members including frontline clinicians, infectious diseases specialists and clinical microbiologists who were members of the IDSA, American Society for Microbiology, 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 coronavirus disease 2019 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 (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 (eg, bronchoscopy) when personal protective equipment (PPE) is limited, and testing is available;
- 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 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 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).

U.S. Preventive Services Task Force Recommendations

The USPSTF (2020) recommendations on screening for BV in pregnancy have stated that:

“The USPSTF recommends against screening for bacterial vaginosis in pregnant persons who are not at increased 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 pregnant persons who are at increased risk for preterm delivery.” (I statement)

KEY WORDS:

Bartonella henselae or quintana, Borrelia burgdorferi, Candida species, Chlamydia pneumonia or trachomatis, Clostridium difficile, Cytomegalovirus (CMV), Enterovirus, Vancomycin-resistant Enterococcus, Gardnerella vaginalis, Hepatitis B, Hepatitis C, Hepatitis G, Herpes simplex virus,

Herpes virus-6, Human immunodeficiency virus 1 (HIV-1), Human immunodeficiency virus (HIV-2), Human papillomavirus (HPV), Influenza virus, Legionella pneumophila, Mycobacterium species, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycoplasma pneumonia, Neisseria gonorrhoeae, Respiratory Viral Panel, Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus, Streptococcus, Group A, Streptococcus, Group B, Trichomonas vaginalis, Human Herpes virus-6, MicroGenDX, MYCODART, BioFire, FilmArray GI Panel, FilmArray Respiratory Panel, GI panel, Respiratory Panel, ePlex, GIPP, BV, Bacterial Vaginosis, Aptima BV Assay, BD Max, Zika Virus, COVID-19, Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, Multitarget

APPROVED BY GOVERNING BODIES:

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.

In October 2016, the Food and Drug Administration completed a review of a de novo request for classification of the BD Max™ Vaginal Panel (Becton, Dickinson). The test was granted class II designation, marketing authorization, and is indicated for the direct detection of DNA targets from bacteria associated with bacterial vaginosis (DEN160001). In 2019, the Aptima BV Assay (Hologic, Inc.) received 510(k) clearance (K190452) with the BD Max as the predicate device. Product code: PQA, NSU, PMN.

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 Act (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

***See Policy Section**

REFERENCES:

1. Adebajo T, Godfred-Cato S, Viens L et al. Update: Interim Guidance for the Diagnosis, Evaluation, and Management of Infants with Possible Congenital Zika Virus Infection - United States, October 2017. MMWR Morb. Mortal. Wkly. Rep., 2017 Oct 20; 66(41).

2. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev.* Apr 2015; 28(2):313-335.
3. Aguirre-Quñonero A, Castillo-Sedano IS, Calvo-Muro F et al. Accuracy of the BD MAX™ vaginal panel in the diagnosis of infectious vaginitis.. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2019 Jan 28; 38(5).
4. Al-Talib H, Latif B, Mohd-Zain Z. Pentaplex PCR assay for detection of hemorrhagic bacteria from stool samples. *J Clin Microbiol.* Sep 2014; 52(9):3244-3249.
5. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am J Med.* Jan 1983; 74(1): 14-22.
6. Anderson NW, Buchan BW, Mayne D, et al. Multicenter clinical evaluation of the illumigene group A Streptococcus DNA amplification assay for detection of group A Streptococcus from pharyngeal swabs. *J Clin Microbiol.* May 2013; 51(5):1474-1477.
7. Andrea SB, Chapin KC. Comparison of Aptima Trichomonas vaginalis transcription-mediated amplification assay and BD affirm VPIII for detection of T. vaginalis in symptomatic women: performance parameters and epidemiological implications. *J Clin Microbiol* 2011; 49(3):866-9.
8. Andrews D, Chetty Y, Cooper BS, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. *BMC Infect Dis.* Oct 10 2017; 17(1): 671.
9. Arora HS, Asmar BI, Salimnia H, et al. Enhanced identification of group B Streptococcus and Escherichia Coli in young infants with meningitis using the Biofire Filmarray Meningitis/Encephalitis Panel. *Pediatr Infect Dis J.* Jul 2017; 36(7):685-687.
10. Barbut F, Monot M, Rousseau A, et al. Rapid diagnosis of Clostridium difficile infection by multiplex real-time PCR. *Eur J Clin Microbiol Infect Dis* 2011; 30(10):1279-85.
11. Beal SG, Tremblay EE, Toffel S, et al. A Gastrointestinal PCR Panel Improves Clinical Management and Lowers Health Care Costs. *J Clin Microbiol.* Jan 2018; 56(1).
12. Beckmann C, Heininger U, Marti H, et al. Gastrointestinal pathogens detected by multiplex nucleic acid amplification testing in stools of pediatric patients and patients returning from the tropics. *Infection.* Dec 2014; 42(6):961-970.
13. Bicmen C, Gunduz AT, Coskun M et al. Molecular detection and identification of mycobacterium tuberculosis complex and four clinically important nontuberculous mycobacterial species in smear-negative clinical samples by the genotype mycobacteria direct test. *J Clin Microbiol* 2011; 49(8):2874-8.
14. Bintsis T. Foodborne pathogens. *AIMS Microbiol.* 2017; 3(3): 529-563.
15. Biswas JS, Al-Ali A, Rajput P, et al. A parallel diagnostic accuracy study of three molecular panels for the detection of bacterial gastroenteritis. *Eur J Clin Microbiol Infect Dis.* Nov 2014; 33(11):2075-2081.
16. Boyanton BL, Jr., Darnell EM, Prada AE, et al. Evaluation of the Lyra Direct Strep Assay to Detect Group A Streptococcus and beta-Hemolytic Groups C/G Streptococcus from Pharyngeal Specimens. *J Clin Microbiol.* Oct 21 2015.

17. Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. *Lancet Respir Med*. May 2017; 5(5): 401-411.
18. Bressollette-Bodin C, Nguyen TV, Illiaquer M, et al. Quantification of two viral transcripts by real time PCR to investigate human herpesvirus type 6 active infection. *J Clin Virol*. Feb 2014; 59(2):94-99.
19. Brittain-Long R, Westin J, Olofsson S et al. Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. *BMC Med* 2011; 9:44.
20. Buchan BW, Olson WJ, Pezewski M, et al. Clinical evaluation of a real-time PCR assay for identification of *Salmonella*, *Shigella*, *Campylobacter* (*Campylobacter jejuni* and *C. coli*), and shiga toxin-producing *Escherichia coli* isolates in stool specimens. *J Clin Microbiol*. Dec 2013; 51(12): 4001-7.
21. Burden of Norovirus Illness in the U.S. Centers for Disease Control and Prevention. <https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html>. Last reviewed March 5, 2021. Accessed May 4, 2021.
22. Cartwright CP, Lembke BD, Ramachandran K, et al. Development and validation of a semiquantitative, multitarget PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol*. Jul 2012; 50(7):2321-2329.
23. Cartwright CP, Pherson AJ, Harris AB, et al. Multicenter study establishing the clinical validity of a nucleic-acid amplification-based assay for the diagnosis of bacterial vaginosis. *Diagn. Microbiol. Infect. Dis.*, 2018 Jun 26; 92(3).
24. Centers for Disease Control and Prevention (CDC). Bacterial Vaginosis (BV) Statistics. 2015; <http://www.cdc.gov/std/bv/stats.htm>. Accessed November 18, 2021.
25. Center for Disease Control and Prevention. *Mycoplasma pneumoniae* Infections: Diagnostic Methods. <https://www.cdc.gov/pneumonia/atypical/mycoplasma/hcp/diagnostic-methods.html>. Accessed May 5, 2021.
26. Center for Disease Control and Prevention. Testing Guidance: Zika Virus. <https://www.cdc.gov/zika/hc-providers/testing-guidance.html>. Accessed May 3, 2021.
27. Chalker VJ, Stocki T, Mentasti M et al. *Mycoplasma pneumoniae* infection in primary care investigated by real-time PCR in England and Wales. *Eur J Clin Microbiol Infect Dis* 2011; 30(7):915-21.
28. Chen HM, Chang TH, Lin FM, et al. Vaginal microbiome variances in sample groups categorized by clinical criteria of bacterial vaginosis.. *BMC Genomics*, 2019 Jan 2; 19(Suppl 10).
29. Choi YJ, Kim HJ, Shin HB et al. Evaluation of peptide nucleic acid probe-based real-time PCR for detection of *Mycobacterium tuberculosis* complex and nontuberculous mycobacteria in respiratory specimens. *Ann Lab Med* 2012; 32(4):257-63.
30. Claas EC, Burnham CA, Mazzulli T, et al. Performance of the xTAG(R) gastrointestinal pathogen panel, a multiplex molecular assay for simultaneous detection of bacterial, viral,

- and parasitic causes of infectious gastroenteritis. *J Microbiol Biotechnol.* 2013; 23(7):1041-1045.
31. Cohen DM, Russo ME, Jaggi P, et al. Multicenter Clinical Evaluation of the Novel Alere i Strep A Isothermal Nucleic Acid Amplification Test. *J Clin Microbiol.* Jul 2015; 53(7):2258-2261.
 32. Committee on Practice Bulletins-Obstetrics, The American College of Obstetricians Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol.* Oct 2012; 120(4):964-973.
 33. Cybulski RJ, Bateman AC, Bourassa L, et al. Clinical Impact of a Multiplex Gastrointestinal Polymerase Chain Reaction Panel in Patients With Acute Gastroenteritis. *Clin Infect Dis.* Nov 13 2018; 67(11): 1688-1696.
 34. Cytomegalovirus (CMV) and Congenital CMV Infection: Laboratory Testing. Centers for Disease Control and Prevention. <https://www.cdc.gov/cmvc/clinical/lab-tests.html>. Page last reviewed April 28, 2020. Accessed May 5, 2021.
 35. Dabisch-Ruthe M, Vollmer T, Adams O et al. Comparison of three multiplex PCR assays for the detection of respiratory viral infections: evaluation of xTAG respiratory virus panel fast assay, RespiFinder 19 assay and RespiFinder SMART 22 assay. *BMC Infect Dis* 2012; 12:163.
 36. de Crom SC, Obihara CC, van Loon AM, et al. Detection of enterovirus RNA in cerebrospinal fluid: comparison of two molecular assays. *J Virol Methods* 2012; 179(1):104-7.
 37. Dhiman, N, Yourshaw, C, Cochanna Turner, MRC, et al (2016). Diagnostic Evaluation of a Multiplex Quantitative Real-Time PCR Assay for Bacterial Vaginosis. *Women's Health Care* 2016, 5:1.
 38. Evaluation of Automatic Class III Designation for FilmArray Meningitis/Encephalitis (ME) Panel Decision Summary. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/reviews/K063765.pdf. Accessed May 5, 2021.
 39. Evaluation of automatic class III designation (de novo) for xTAG gastrointestinal pathogen panel (GPP) decision summary. Food and Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/reviews/K121454.pdf. Accessed May 3, 2021.
 40. Faron ML, Ledeboer NA, Granato P, et al. Detection of Group A Streptococcus in Pharyngeal Swab Specimens Using the AmpliVue GAS Isothermal Helicase-Dependent Amplification Assay. *J Clin Microbiol.* May 13 2015.
 41. Filkins L, Hauser J, Robinson-Dunn B, Tibbetts R, Boyanton B, Revell P. Guidelines for the Detection and Identification of Group B Streptococcus. American Society for Microbiology. Published 3/10/20. <https://asm.org/ASM/media/Policy-and-Advocacy/images/ASM-GBS-guideline-031020.pdf?ext=.pdf>. Accessed May 5, 2021.
 42. Food and Drug Administration. Evaluation of Automatic Class III Designation For BD Max Vaginal Panel: Decision Summary. 2016;https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160001.pdf. Accessed November 18, 2021.

43. Freeman K, Mistry H, Tsertsvadze A, et al. Multiplex tests to identify gastrointestinal bacteria, viruses and parasites in people with suspected infectious gastroenteritis: a systematic review and economic analysis. *Health Technol Assess.* Apr 2017; 21(23): 1-188.
44. Gaspar C, Palmeira-de-Oliveira R, Martinez-de-Oliveira J, et al. Development and validation of a new one-step Multiplex-PCR assay for the detection of ten *Lactobacillus* species. *Anaerobe*, 2019 Jun 18; 59:192-200.
45. *Gastrointestinal Tract Infections.*
https://www.uib.cat/depart/dba/microbiologia/ADSenfcomI/material_archivos/infeccion%20gastrointestinal.pdf. Accessed May 5, 2021.
46. Gaydos CA, Beqaj S, Schwebke JR, et al. Clinical Validation of a Test for the Diagnosis of Vaginitis. *Obstet Gynecol.* Jul 2017; 130(1):181-189.
47. Gazi H, Degerli K, Kurt O et al. Use of DNA hybridization test for diagnosing bacterial vaginosis in women with symptoms suggestive of infection. *APMIS* 2006; 114(11):784-7.
48. Giulieri SG, Chapuis-Taillard C, Manuel O, et al. Rapid detection of enterovirus in cerebrospinal fluid by a fully-automated PCR assay is associated with improved management of aseptic meningitis in adult patients. *J Clin Virol.* Jan 2015; 62:58-62.
49. GRADE. The GRADE Working Group. <https://www.gradeworkinggroup.org/>. Accessed January 8, 2019.
50. Graf EH, Farquharson MV, Cardenas AM. Comparative evaluation of the FilmArray meningitis/encephalitis molecular panel in a pediatric population. *Diagn Microbiol Infect Dis.* Jan 2017; 87(1):92-94.
51. Hall AJ, Vinje J, Lopman B, et al. Updated Norovirus Outbreak Management and Disease Prevention Guidelines. *CDC MMWR.* Published 3/4/11.
<https://www.cdc.gov/mmwr/pdf/rr/rr6003.pdf>. Accessed November 17, 2019.
52. Hammerschlag MR, Kohlhoff SA. Treatment of chlamydial infections. *Expert Opin Pharmacother* 2012; 13(4):545-52.
53. Hanson KE, Slechta ES, Killpack JA, et al. Preclinical Assessment of a fully automated multiplex PCR panel for detection of central nervous system pathogens. *J Clin Microbiol.* Mar 2016; 54(3):785-787.
54. He T, Kaplan S, Kamboj M, et al. Laboratory Diagnosis of Central Nervous System Infection. *Curr Infect Dis Rep.* Nov 2016; 18(11): 35.
55. Henson AM, Carter D, Todd K, et al. Detection of *Streptococcus pyogenes* by use of Illumigene group A *Streptococcus* assay. *J Clin Microbiol.* Dec 2013; 51(12):4207-4209.
56. Hilbert DW, Smith WL, Chadwick SG, et al. Development and validation of a highly accurate quantitative real-time PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol.* Apr 2016; 54(4):1017-1024.
57. Hopkins MJ, Smith G, Hart IJ et al. Screening tests for *Chlamydia trachomatis* or *Neisseria gonorrhoeae* using the cobas 4800 PCR system do not require a second test to confirm: an audit of patients issued with equivocal results at a sexual health clinic in the Northwest of England, U.K. *Sex Transm Infect* 2012; 88(7):495-7.

58. Huang HS, Tsai CL, Chang J, et al. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. *Clin Microbiol Infect.* Oct 2018; 24(10): 1055-1063.
59. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19. Published December 23, 2020. <https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/>. Accessed on May 5, 2021.
60. IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press.
61. Ishiguro N, Koseki N, Kaiho M, et al. Sensitivity and Specificity of a Loop-Mediated Isothermal Amplification Assay for the Detection of Mycoplasma Pneumonia from Nasopharyngeal Swab Samples Compared with those of Real-time PCR. *Clin Lab.* 2015; 61(5-6):603-606.
62. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for use in genitourinary medicine clinics. *Sex Transm Infect.* Dec 2002; 78(6): 413-5.
63. Izumikawa K, Izumikawa K, Takazono T, et al. Clinical features, risk factors and treatment of fulminant Mycoplasma pneumoniae pneumonia: a review of the Japanese literature. *J Infect Chemother.* Mar 2014; 20(3):181-185.
64. Jiang Y, Fang L, Shi X, et al. Simultaneous detection of five enteric viruses associated with gastroenteritis by use of a PCR assay: a single real-time multiplex reaction and its clinical application. *J Clin Microbiol.* Apr 2014; 52(4):1266-1268.
65. Khare R, Espy MJ, Cebelinski E, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. *J Clin Microbiol.* Oct 2014; 52(10):3667-3673.
66. Khare R, Espy MJ, Cebelinski E, et al. Multiplex Detection of Gastrointestinal Pathogens: A Comparative Evaluation of Two Commercial Panels Using Clinical Stool Specimens. *J Clin Microbiol.* Aug 6 2014.
67. Kimberlin DW, Brady MT, Jackson, MA, et al. *Redbook 2018*. Am Acad Peds.
68. Knetsch CW, Bakker D, de Boer RF et al. Comparison of real-time PCR techniques to cytotoxigenic culture methods for diagnosing Clostridium difficile infection. *J Clin Microbiol* 2011; 49(1):227-31.
69. Kosai K, Suzuki H, Tamai K, et al. Multicenter evaluation of Verigene Enteric Pathogens Nucleic Acid Test for detection of gastrointestinal pathogens. *Sci Rep.* Feb 04 2021; 11(1): 3033.
70. Kusters JG, Reuland EA, Bouter S, et al. A multiplex real-time PCR assay for routine diagnosis of bacterial vaginosis. *Eur J Clin Microbiol Infect Dis.* Sep 2015; 34(9):1779-1785.
71. Lamont RF, Sobel JD, Akins RA, et al. The vaginal microbiome: new information about genital tract flora using molecular-based techniques. *BJOG.* Apr 2011; 118(5):533-549.
72. Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. *Am J Obstet Gynecol.* Apr 2004; 190(4): 1004-10.

73. Lassauniere R, Kresfelder T, Venter M. A novel multiplex real-time RT-PCR assay with FRET hybridization probes for the detection and quantitation of 13 respiratory viruses. *J Virol Methods* 2010; 165(2):254-60.
74. Launes C, Casas-Alba D, Fortuny C, et al. Utility of FilmArray meningitis/encephalitis panel during outbreak of brainstem encephalitis caused by enterovirus in Catalonia in 2016. *J Clin Microbiol.* Jan 2017; 55(1):336-338.
75. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of biofire filmarray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol.* Sep 2016; 54(9):2251-2261.
76. Leclair CM. Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. *Obstet Gynecol.* Jan 2020; 135(1): e1-e17.
77. Liveris D, Schwartz I, McKenna D et al. Comparison of five diagnostic modalities for direct detection of *Borrelia burgdorferi* in patients with early Lyme disease. *Diagn Microbiol Infect Dis* 2012; 73(3):243-5.
78. Lynch T, Peirano G, Lloyd T, et al. Molecular Diagnosis of Vaginitis: Comparing Quantitative PCR and Microbiome Profiling Approaches to Current Microscopy Scoring. *J. Clin. Microbiol.*, 2019 Jul 19; 57(9).
79. MacCannell T, Umscheil CA, Agarwal RK, et al. Guideline for the Prevention and Control of Norovirus Gastroenteritis Outbreaks in Healthcare Settings. CDC. Updated 2/15/17. <https://www.cdc.gov/infectioncontrol/pdf/guidelines/norovirus-guidelines.pdf>. Accessed May 5, 2021
80. Mansuy JM, Mengelle C, Da Silva I et al. Performance of a rapid molecular multiplex assay for the detection of influenza and picornaviruses. *Scand J Infect Dis* 2012; 44(12):963-8.
81. Marangoni A, Foschi C, Nardini P et al. Evaluation of the new test VERSANT CT/GC DNA 1.0 assay for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens. *J Clin Lab Anal* 2012; 26(2):70-2.
82. Maurin M, Hammer L, Gestin B et al. Quantitative real-time PCR tests for diagnostic and prognostic purposes in cases of legionellosis. *Clin Microbiol Infect* 2010; 16(4):379-84.
83. Mentasti M, Fry NK, Afshar B, et al. Application of *Legionella pneumophila*-specific quantitative real-time PCR combined with direct amplification and sequence-based typing in the diagnosis and epidemiological investigation of Legionnaires' disease. *Eur J Clin Microbiol Infect Dis.* Aug 2012; 31(8):2017-2028.
84. Messacar K, Breazeale G, Robinson CC, et al. Potential clinical impact of the film array meningitis encephalitis panel in children with suspected central nervous system infections. *Diagn Microbiol Infect Dis.* Sep 2016; 86(1):118-120.
85. McDonald LC, Gerding DN, Johnson S et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin. Infect. Dis.*, 2018 Feb 21; 66(7).
86. Miller JM, Binnicker MJ, Campbell S et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases

Society of America and the American Society for Microbiology. Clin. Infect. Dis., 2018 Jun 30; 67(6).

87. Miyashita N, Kawai Y, Inamura N, et al. Setting a standard for the initiation of steroid therapy in refractory or severe Mycoplasma pneumoniae pneumonia in adolescents and adults. J Infect Chemother. Mar 2015; 21(3):153-160.
88. Munson E, Napierala M, Basile J et al. Trichomonas vaginalis transcription-mediated amplification-based analyte-specific reagent and alternative target testing of primary clinical vaginal saline suspensions. Diagn Microbiol Infect Dis 2010; 68(1):66-72.
89. National Institute for Health and Care Excellence (NICE). Clinical Guideline: Antenatal Care for Uncomplicated Pregnancies [CG62]. 2008; <https://www.nice.org.uk/guidance/cg62/>. Updated February 4, 2019. Accessed November 18, 2021.
90. Nellore A, Huprikar S. Vancomycin-resistant Enterococcus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant, 2019 Mar 27; 33(9).
91. NIH Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Updated May 26, 2020. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Accessed on May 5, 2021.
92. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. Feb 1991; 29(2): 297-301.
93. Olson D, Watkins LK, Demirjian A, et al. Outbreak of Mycoplasma pneumoniae-Associated Stevens-Johnson Syndrome. Pediatrics. Aug 2015; 136(2):e386-394.
94. Onori M, Coltella L, Mancinelli L, et al. Evaluation of a multiplex PCR assay for simultaneous detection of bacterial and viral enteropathogens in stool samples of paediatric patients. Diagn Microbiol Infect Dis. Jun 2014; 79(2):149-154.
95. Pappas PG, Kauffman CA, Andes DR et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin. Infect. Dis., 2015 Dec 19; 62(4).
96. Pierce VM, Hodinka RL. Comparison of the GenMark Diagnostics eSensor respiratory viral panel to real-time PCR for detection of respiratory viruses in children. J Clin Microbiol 2012; 50(11):3458-65.
97. Puopolo KM, Lynfield R, Cummings JJ et al. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics, 2019 Jul 10; 144(2).
98. Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae 2014. CDC MMWR. Published 3/14/14. <https://www.cdc.gov/std/laboratory/2014labrec/2014-lab-rec.pdf>. Accessed May 5, 2021.
99. Rhein J, Bahr NC, Hemmert AC, et al. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. Diagn Microbiol Infect Dis. Mar 2016; 84(3):268-273.

100. Richter SS, Otiso J, Goje OJ, et al. Prospective Evaluation of Molecular Assays for Diagnosis of Vaginitis. *J Clin Microbiol.* Dec 23 2019; 58(1).
101. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. *Am. J. Gastroenterol.*, 2016 Apr 14; 111(5).
102. Rumyantseva T, Shipitsyna E, Guschin A, et al. Evaluation and subsequent optimizations of the quantitative AmpliSens Florocenosis/Bacterial vaginosis-FRTmultiplex real-time PCR assay for diagnosis of bacterial vaginosis. *Apmis.* Dec 2016; 124(12):1099-1108.
103. Rumyantseva TA, Bellen G, Romanuk TN, et al. Utility of microscopic techniques and quantitative real-time polymerase chain reaction for the diagnosis of vaginal microflora alterations. *J Low Genit Tract Dis.* Jul 11 2014.
104. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* Apr 2012; 137(4):516-542.
105. Sattar SBA, Singh S. Bacterial Gastroenteritis. [Updated 2020 Aug 11]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK513295/>. Accessed May 5, 2021.
106. Schwebke JR, Gaydos CA, Nyirjesy P, et al. Diagnostic Performance of a Molecular Test versus Clinician Assessment of Vaginitis. *J. Clin. Microbiol.*, 2018 Apr 13; 56(6).
107. Schwebke JR, Hobbs MM, Taylor SN et al. Molecular testing for *Trichomonas vaginalis* in women: results from a prospective U.S. clinical trial. *J Clin Microbiol* 2011; 49(12):4106-11.
108. Schwebke JR, Taylor SN, Ackerman R, et al. Clinical Validation of the Aptima Bacterial Vaginosis and Aptima Candida/*Trichomonas* Vaginitis Assays: Results from a Prospective Multicenter Clinical Study. *J Clin Microbiol.* Jan 28 2020; 58(2).
109. Seagar AL, Neish B, Laurenson IF. Comparison of two in-house real-time PCR assays with MTB Q-PCR Alert and GenoType MTBDRplus for the rapid detection of mycobacteria in clinical specimens. *J Med Microbiol* 2012; 61(Pt 10):1459-64.
110. Shane AL, Mody RK, Crump JA et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. *Clin. Infect. Dis.*, 2017 Oct 21; 65(12).
111. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* Nov 15 2012; 55(10):e86-102.
112. Slinger R, Goldfarb D, Rajakumar D et al. Rapid PCR detection of group A *Streptococcus* from flocculated throat swabs: a retrospective clinical study. *Ann Clin Microbiol Antimicrob* 2011; 10:33.
113. Stanek G, Wormser GP, Gray J et al. Lyme borreliosis. *Lancet* 2012; 379(9814):461-73.
114. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire(R) FilmArray(R) meningitis/encephalitis panel: a systematic review and meta-analysis. *Clin Microbiol Infect.* Mar 2020; 26(3): 281-290.

115. Thompson A, Timm K, Borders N, et al. Diagnostic performance of two molecular assays for the detection of vaginitis in symptomatic women.. Eur. J. Clin.Microbiol. Infect. Dis., 2019 Sep 11.
116. Tsai JD, Tsai HJ, Lin TH, et al. Comparison of the detection rates of RT-PCR and virus culture using a combination of specimens from multiple sites for enterovirus-associated encephalomyelitis during enterovirus 71 epidemic. Jpn J Infect Dis. 2014; 67(5):333-338.
117. Tunkel AR, Hasbun R, Bhimraj A et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare- Associated Ventriculitis and Meningitis.. Clin. Infect. Dis., 2017 Feb 17; 64(6).
118. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. CDC MMWR. Published 1/16/09.
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm?s_cid=mm5801a3_e. Accessed May 5, 2021.
119. Upton A, Bissessor L, Farrell E, et al. Comparison of illumigene Group A Streptococcus assay with culture of throat swabs from children with sore throats in the New Zealand school-based rheumatic fever prevention program. J Clin Microbiol. Nov 11 2015.
120. U.S. Preventive Services Task Force. Bacterial Vaginosis in Pregnancy to Prevent Preterm Delivery: Screening. 2019;<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/bacterial-vaginosis-in-pregnant-adolescents-and-women-to-prevent-preterm-delivery-screening>. Accessed November 19, 2021.
121. van den Munckhof EHA, van Sitter RL, Boers KE, et al. Comparison of Amsel criteria, Nugent score, culture and two CE-IVD marked quantitative real-time PCRs with microbiota analysis for the diagnosis of bacterial vaginosis. Eur. J. Clin. Microbiol. Infect. Dis., 2019 Mar 25; 38(5).
122. Van Der Pol B, Daniel G, Kodsi S, et al. Molecular-based Testing for Sexually Transmitted Infections Using Samples Previously Collected for Vaginitis Diagnosis. Clin. Infect. Dis., 2018 Aug 8; 68(3).
123. van der Veer C, van Houdt R, van Dam A, et al. Accuracy of a commercial multiplex PCR for the diagnosis of bacterial vaginosis. J Med Microbiol. Sep 2018; 67(9): 1265-1270.
124. Verani JR, McGee L, Schrag SJ, et al. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. Nov 19 2010; 59(RR-10):1-36.
125. Wheeler CM, Hunt WC, Cuzick J, et al. The influence of type-specific human papillomavirus infections on the detection of cervical precancer and cancer: A population-based study of opportunistic cervical screening in the United States. Int J Cancer. Aug 1 2014; 135(3):624-634.
126. Wootton SH, Aguilera E, Salazar L, et al. Enhancing pathogen identification in patients with meningitis and a negative Gram stain using the BioFire FilmArray ((R)) Meningitis/Encephalitis panel. Ann Clin Microbiol Antimicrob. Apr 21 2016; 15:26.
127. Workowski KA, Bolan GA, Centers for Disease Control and Prevention, et al. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. Jun 5 2015; 64(RR-03):1-137.

128. Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. Obstet Gynecol. Jan 2020; 135(1): e1-e17.
129. van den Munckhof EHA, van Sitter RL, Boers KE, et al. Comparison of Amsel criteria, Nugent score, culture and two CE-IVD marked quantitative real-time PCRs with microbiota analysis for the diagnosis of bacterial vaginosis. Eur J Clin Microbiol Infect Dis. May 2019; 38(5): 959-966.
130. van der Veer C, van Houdt R, van Dam A, et al. Accuracy of a commercial multiplex PCR for the diagnosis of bacterial vaginosis. J Med Microbiol. Sep 2018; 67(9):1265-1270.
131. Xia QF, Liu JB, Liu P et al. Development of a novel quantitative real-time assay using duplex mutation primers for rapid detection of Candida species. Mol Med Rep 2012; 5(1):207-10.

POLICY HISTORY:

Adopted for Blue Advantage, November 12, 2018.

Medical Policy Group, January 2020

Medical Policy Group, March 2021

Medical Policy Group, June 2021

Medical Policy Group, November 2021: 2022 Annual Coding Update. Added new CPT codes 0301U, 0302U, 87154 to policy section.

Medical Policy Group, December 2021

Medical Policy Group, March 2022: Quarterly coding update. Added new CPT code 0321U to policy section.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.