BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Identification of Microorganisms Using Nucleic Acid Probes

Policy #: 548
Latest Review Date: January 2024
Category: Laboratory

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 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 March 1, 2024

For nucleic acid probe panel testing, see LCD L38988/Article A58710.

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
- BK polyomavirus (BKPyV, Human polyomavirus 1)
- Candida species
- Chlamydia pneumoniae
- Chlamydia trachomatis
- Clostridium difficile
- Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
- Enterovirus
- Gardnerella vaginalis
- Herpes simplex virus
- Human papillomavirus
- Influenza virus
- Legionella pneumophila
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma genitalium
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae
- Orthopoxvirus (Monkeypox)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Staphylococcus aureus
- Staphylococcus aureus, methicillin-resistant
- Streptococcus, group A
- Streptococcus, group B
- Tick-borne bacteria
- 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

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

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:

- Infectious Disease (fungus and/or bacteria) Panel

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** to test for BK polyomavirus in renal transplant recipients receiving immunosuppressive therapy.

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** to test for BK polyomavirus in persons with renal failure in the setting of an immunosuppressed state (including but not limited to persons with a history of solid organ transplant on immunosuppressive therapy, history of hematopoietic cell transplantation, hematologic malignancy, HIV, or autoimmune disease on immunosuppressive therapy).

CURRENT CODING:

CPT Codes CODES:

The table below lists CPT Codes for various nucleic acid probes.

Table. CPT Codes for Nucleic Acid Probes

Pathogen	Direct Probe	Amplified Probe	Quantification
Anaplasma phagocytophilum		87468 (Med Nec)	
Babesia microti		87469 (Med Nec)	
Bartonella henselae or quintan[a]		87471 (Med Nec)	87472 (Inv) 0301U, 0302U (Inv)
BK polyomavirus	87797 (Med Nec)	87797 (Med Nec)	87797 (Med Nec)

Bloodstream pathogen identification		87154 (Med Nec)	
Borrelia borgdorferi[a]	87475 (Med Nec)	87476 (Med Nec)	
Borrelia miyamotoi		87478 (Med Nec)	
Candida species	87480 (Med Nec)	87481 (Med Nec) 0068U (Med Nec)	87482 (Inv)
Central Nervous System Pathogen Panel		87483 (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)
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 (Med Nec) 87624-87625 (Med Nec) 0429U (Med Nec)	0096U (Med Ned) 0354U (Med Nec)- **(Deleted 4/1/2024)**
Infectious Agent detection and identification		0370U (Inv)	0112U (Inv)
Infectious disease		0140U-0142U (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 genitalium		8763 (Med Nec) 0402U (Med Nec)	
Mycoplasma pneumoniae	87580 (Med Nec)	87581 (Med Nec)	87582 (Inv)
Neisseria gonorrhoeae	87590 (Med Nec)	87591 (Med Nec)	87592 (Inv)
Orthopoxvirus (Monkeypox)		87593 (Med Nec)	
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[c]		87635 (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 87800	87798 87801	87799
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 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.
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 April 17, 2022, to February 28, 2024

For nucleic acid probe panel testing, see LCD L38988/Article A58710.

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
- Influenza virus
- Legionella pneumophila
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma genitalium
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae

- Orthopoxvirus (Monkeypox)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Staphylococcus aureus
- Staphylococcus aureus, methicillin-resistant
- Streptococcus, group A
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- Tick-borne bacteria
- 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

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

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:

- Infectious Disease (fungus and/or bacteria) Panel

CURRENT CODING:

CPT Codes 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
Anaplasma phagocytophilum		87468 (Med Nec)	
Babesia microti		87469 (Med Nec)	

Bartonella henselae or quintan[a]		87471 (Med Nec)	87472 (Inv) 0301U, 0302U (Inv)
Bloodstream pathogen identification		87154 (Med Nec)	
Borrelia borgdorferi[a]	87475 (Med Nec)	87476 (Med Nec)	
Borrelia miyamotoi		87478 (Med Nec)	
Candida species	87480 (Med Nec)	87481 (Med Nec) 0068U (Med Nec)	87482 (Inv)
Central Nervous System Pathogen Panel		87483 (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)
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)
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Human Papillomavirus (HPV)		87623 (Med Nec) 87624-87625 (Med Nec) 0429U (Med Nec)	0096U (Med Ned) 0354U (Med Nec)- **(Deleted 4/1/2024)**
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Mycobacterium tuberculosis	87555 (Med Nec)	87556 (Med Nec)	87557 (Inv)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[c]		87635 (Med Nec)	
Staphylococcus aureus		87640 (Med Nec)	
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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 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.
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 April 1, 2020, to April 16, 2022
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
- Influenza virus
- Legionella pneumophila
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
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Candida species[b]	87480 (Med Nec)	87481 (Med Nec) 0068U (Med Nec)	87482 (Inv)
Central Nervous System Pathogen Panel		87483 (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)		
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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)
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)
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Human Papillomavirus (HPV)		87623(Med Nec) 87624-87625 (Med Nec)	0096U (Med Nec) 0354U (Med Nec)-**(Deleted 4/1/2024)**
Infectious Agent detection and identification			0112U (Inv)
Infectious disease		0140U-0142U (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)
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Staphylococcus aureus		87640 (Med Nec)	
Staphylococcus aureus, methicillin-resistant		87641 (Med Nec)	
Streptococcus group A[d]	87650 (Med Nec)	87651 (Med Nec)	87652 (Inv)
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Unlisted (infectious agent detection by nucleic acid (DNA or RNA, not otherwise specified)[f]	87797 87800	87798 87801	87799
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 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.
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

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 their 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 reactions. 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 using 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 as 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 following:

- The presence of Lactobacillus species, plus G. vaginalis at least 6.0 log cells/mL, and/or the 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 the 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 the 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 changes 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 changes in disease status. The systematic review reported that all three reviewed multiplex PCR systems were highly accurate. One RCT and one quasi-RCT evaluated the 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 that 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 persons>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. However, 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. Suppose a pregnant woman (with risk of Zika virus exposure) has a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection. In that case, 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, are 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 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 to 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 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 for 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 weeks, 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 is 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 viruses 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 pre-agreed 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 the use of "a NAAT alone or a multistep algorithm for testing…rather than a toxin test alone when there are pre-agreed 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 (e.g., bronchoscopy) when personal protective equipment (PPE) is limited and testing is available;
- asymptomatic individuals without known exposure when the results will impact isolation/quarantine/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 swabs, anterior nasal swabs, 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 the member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:
***See Policy Section**

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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, and 87154 to the policy section.

Medical Policy Group, December 2021
Medical Policy Group, March 2022: Quarterly coding update.
Medical Policy Group, June 2022
Medical Policy Group, October 2022: Quarterly coding update.
Medical Policy Group, December 2022
Medical Policy Group, June 2023
Medical Policy Group, January 2024: Policy statement updated to include BK polyomavirus as medically necessary for renal transplant recipients receiving immunosuppressive therapy and in persons with renal failure in the setting of an immunosuppressed state. Available for comment from February 1, 2024, through March 1, 2024.
Medical Policy Group, March 2024: Quarterly Coding Update. CPT codes 0354U deleted effective 4/1/2024.
