



# Louisiana

## Identification of Microorganisms Using Nucleic Acid Probes

**Policy #** 00488

Original Effective Date: 10/21/2015

Current Effective Date: 05/01/2018

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

### When Services May Be Eligible for Coverage

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

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

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

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

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

- Cytomegalovirus

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

### **When Services Are Considered Investigational**

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

Based on review of available data, the Company considers the use of nucleic acid testing using a direct or amplified probe technique with or without quantification of viral load to be **investigational\*** for the following microorganisms:

- All other microorganisms not listed above
- Chlamydomphila pneumoniae
- Hepatitis G virus
- Gastrointestinal pathogen panel
- Central nervous system pathogen panel and all other panels with multiple nucleic acid probe testing, except for a respiratory virus panel

### **Policy Guidelines and Coding**

It should be noted that the technique for quantification includes both amplification and direct probes; therefore, simultaneous coding for both quantification with either amplification or direct probes, is not warranted.

Antibiotic sensitivity of streptococcus A cultures is generally not performed for throat cultures. However, if an antibiotic sensitivity is considered, then the most efficient method of diagnosis would be a combined culture and antibiotic sensitivity.

For uncomplicated infections, testing for only 1 candida species, *Candida 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 (2010) classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or likely to be *C. albicans*; or in nonimmunocompromised 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.

In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared with traditional culture techniques is the rapidity of results. This advantage suggests that the most

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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.

Many probes have been combined into panels of tests. For the purposes of this policy, other than the gastrointestinal pathogen panel, central nervous system panel, and the respiratory virus panel, only individual probes are reviewed.

**Table PG1. CPT Codes for Nucleic Acid Probes**

Pathogen	Direct Probe	Amplified Probe	Quantification
<i>Bartonella henselae</i> or <i>quintana</i>		87471	87472
<i>Candida</i> species	87480	87481	87482
<i>Chlamydophila pneumoniae</i>	87485	87486	87487
<i>Chlamydia trachomatis</i>	87490	87491	87492
<i>Clostridium difficile</i>	87493		
<i>Cytomegalovirus</i>	87495	87496	87497
<i>Enterococcus</i> , vancomycin-resistant (eg, <i>enterococcus vanA</i> , <i>vanB</i> )		87500	
<i>Enterovirus</i>		87498	
<i>Gardnerella vaginalis</i>	87510	87511	87512
Gastrointestinal pathogen panel		87505-87507	
Central nervous system pathogen panel		87483 effective 01/01/17	
Hepatitis B virus		87516	87517
Hepatitis C virus	87520	87521	87522
Hepatitis G virus	87525	87526	87527
Herpes simplex virus	87528	87529	87530
Herpes virus-6	87531	87532	87533
HIV-1	87534	87535	87536
HIV-2	87537	87538	87539
Human papillomavirus		87623-87625	
Influenza virus		87501-87503	
<i>Legionella pneumophila</i>	87540	87541	87542
Mycobacteria species	87550	87551	87552
<i>Mycobacterium tuberculosis</i>	87555	87556	87557
<i>Mycobacterium avium-intracellulare</i>	87560	87561	87562
<i>Mycoplasma pneumoniae</i>	87580	87581	87582
<i>Neisseria gonorrhoeae</i>	87590	87591	87592
Respiratory virus panel		87631-87633	
<i>Staphylococcus aureus</i>		87640	
<i>Staphylococcus aureus</i> , methicillin-resistant		87641	
<i>Streptococcus</i> , group A	87650	87651	87652
<i>Streptococcus</i> , group B		87653	
<i>Trichomonas vaginalis</i>	87660	87661	

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CPT codes 87797, 87798, and 87799 describe the use of direct probe, amplified probe, and quantification, respectively, for infectious agents not otherwise specified. A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy.

### **Background/Overview**

#### **MICROORGANISMS AND CLINICAL DISEASE**

Various bacteria, viruses, and fungi that can cause clinical disease and can be detected with various nucleic acid probe techniques are briefly outlined below.

#### ***Bartonella henselae* or *quintana***

*Bartonella henselae* is responsible for the cat-scratch disease. In most patients (90%-95%), the infection is a localized skin and lymph node disorder that occurs close to the site of inoculation and is characterized by chronic regional lymphadenopathy that develops about 2 weeks after contact with a cat. Less commonly, *Bartonella henselae* infection may lead to disseminated infection, which can manifest as visceral organ involvement, often with fever and hepatosplenomegaly, a variety of ocular manifestations, and neurological manifestations (most commonly, encephalopathy).

*Bartonella* may also cause an opportunistic infection in HIV-infected patients, in whom it is characterized by an acute febrile bacteremic illness, evolving to an asymptomatic bacteremia and finally indolent vascular skin lesions. The organism is typically detected using culture techniques, although an incubation period of 5 to more than 30 days is required. DNA probe technology has been investigated as a diagnostic technique.

*Bartonella quintana* has classically been associated with "trench fever," which is characterized by systemic symptoms (bone pain, malaise, headache), along with recurring fevers of varying durations. Among HIV-infected patients, *B. quintana* has been associated with bacillary angiomatosis.

*Bartonella* are fastidious organisms, making culture difficult. Histology of lesions affected by bacillary angiomatosis may be characteristic. Histology of affected lymph nodes or other tissue with *B. henselae* may demonstrate findings that are suggestive of cat-scratch disease, but which may be seen in other conditions. Two antigenic methods are available, one using indirect fluorescence assay and one using enzyme immunosorbent assay, for both *B. henselae* and *B. quintana* infections. A positive serologic test is generally considered supportive, but not definitive, for *Bartonella* infection. Serologic methods may have limited yield in immunosuppressed patients.

#### ***Candida* Species**

A commonly occurring yeast, *Candida* species normally can be found on the diseased skin, throughout the entire gastrointestinal tract, expectorated sputum, the female genitalia, and in the urine of patients with indwelling Foley catheters. Clinically significant *Candida* infections are typically diagnosed by clinical observation or by identification of the yeast forms on biopsy specimens. *Candida* species are a common cause of vaginitis.

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### ***Chlamydophila pneumoniae***

*Chlamydophila pneumoniae* is an important cause of pneumonia, bronchitis, and sinusitis. Culture and isolation of the microorganism are difficult; a micro-immunofluorescence serum test may be used. The use of polymerase chain reaction amplification now offers a rapid diagnosis.

### ***Chlamydia trachomatis***

*Chlamydia trachomatis* is a significant intracellular pathogen causing, most prominently, urogenital disease (including pelvic inflammatory disease) and perinatal infections.

*C. trachomatis* is also responsible for lymphogranuloma venereum. Due to its prevalence and association with pelvic inflammatory disease and perinatal disease, widespread testing of chlamydia is recommended; routine chlamydia testing has been adopted as a quality measure by Healthcare Effectiveness Data and Information Set. This microorganism can be diagnosed by (1) identifying the typical intracytoplasmic inclusions in cytology specimens; (2) isolation in tissue culture; (3) demonstration of chlamydial antigen by enzyme-linked immunosorbent assay or by immunofluorescent staining; or (4) demonstration of DNA using a direct probe or amplification technique.

### **Cytomegalovirus**

Cytomegalovirus (CMV) is a common virus, but rarely causes clinical disease in healthy individuals. However, this virus can cause protean disease syndromes, most prominently in immunosuppressed patients, including transplant recipients or those infected with HIV. CMV can also remain latent in tissues after recovery of the host from an acute infection. Diagnosis depends on the demonstration of the virus or viral components or demonstration of a serologic rise. DNA probe techniques, including amplification, have also been used to identify patients at-risk of developing CMV disease as a technique to triage antiviral therapy.

### ***Clostridium difficile***

*Clostridium difficile* is an anaerobic, toxin-producing bacteria present in the intestinal tract. It causes clinical colitis when the normal intestinal flora is altered, and overgrowth of *C. difficile* occurs. The common precipitant that disrupts the normal intestinal flora is previous treatment with antibiotics. The disorder has varying severity but can be severe and in extreme cases, life-threatening. *C. difficile* is easily spread by person-to-person contact and is a common cause of hospital-acquired outbreaks. Hospital infection-control measures, such as wearing gloves and handwashing with soap and water, are effective methods of reducing the spread of *C. difficile*. The standard diagnosis is made by an assay for the *C. difficile* cytotoxin or by routine culture methods.

### **Enterovirus**

Enteroviruses are single-stranded RNA viruses. This group of viruses includes the polioviruses, coxsackieviruses, echoviruses, and other enteroviruses. In addition to 3 polioviruses, there are more than 60 types of non-polio enteroviruses that can cause disease in humans. Most people who are infected with a non-polio *enterovirus* have no disease symptoms. Infected persons who develop illness usually develop

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either mild upper respiratory symptoms, flu-like symptoms with fever and muscle aches, or an illness with rash. Less commonly, enteroviruses can cause “aseptic” or viral meningitis, encephalitis, acute paralysis, and/or myocarditis. Enteroviral infections can cause life-threatening systemic infections in neonates, which are often associated with myocarditis or fulminant hepatitis. The use of amplified probe DNA test(s) can be used to detect enteroviruses.

### ***Gardnerella vaginalis***

A common microorganism, *Gardnerella vaginalis* is typically found in the human vagina and is usually asymptomatic. However, *G. vaginalis* is found in virtually all women with bacterial vaginosis and is characterized by inflammation and perivaginal irritation. The microorganism is typically identified by culture. The role of *G. vaginalis* in premature rupture of membranes and preterm labor is also under investigation.

### **Hepatitis B, C, and G**

Hepatitis is typically diagnosed by a pattern of antigen and antibody positivity. However, the use of probe technology permits the direct identification of hepatitis DNA or RNA, which may also provide prognostic information. Quantification techniques are used to monitor the response to direct-acting antiviral, interferon, and/or ribavirin therapy in patients with hepatitis C.

### **Herpes Simplex Virus**

Herpes simplex infection of the skin and mucous membranes is characterized by a thin-walled vesicle on an inflammatory base typically in the perioral, ocular, or genital area, although any skin site may be involved. The diagnosis may depend on a pathologic examination of cells scraped from a vesicle base or by tissue culture techniques. Herpes simplex encephalitis is one of the most common and serious sporadic encephalitides in immunocompetent adults. The polymerase chain reaction technique to detect herpes simplex virus in the cerebrospinal fluid has been used to provide a rapid diagnosis of herpes virus encephalitis.

### **Human Herpesvirus 6**

Human herpesvirus 6 (HHV-6) is the common collective name for HHV-6A and HHV-6B. These closely related viruses are 2 of the 9 herpesviruses known to have humans as their primary host. HHV-6 is widespread in the general population. In immunocompetent hosts, HHV-6 primary infection typically causes a mild, self-limited illness in childhood, often roseola. HHV-6 may also cause meningitis and encephalitis in children and adults. Diagnosis is typically based on rising serologic titers.

In immunosuppressed patients, HHV-6 reactivation may cause meningitis, encephalitis, pneumonitis, and/or bone marrow suppression.

### **HIV-1 and HIV-2**

DNA probe technology for HIV-1 is widely disseminated, and HIV-1 quantification has become a standard laboratory test in HIV-1 infected patients. HIV-2 can result in severe immunosuppression and the development of serious opportunistic diseases. Although HIV-2 has been reported in the United States, it is

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most commonly found in Western Africa. Blood donations are routinely tested for HIV-2, but due to its rarity in this country, clinical testing for HIV-2 is typically limited to those in contact with persons in a country where HIV-2 is endemic or when the clinical picture suggests HIV infection, but testing for HIV-1 is negative.

### **Influenza Virus**

Influenza virus is a very common pathogen that accounts for a high burden of morbidity and mortality, especially in elderly and immunocompromised patients. The most common means of identifying influenza is by viral culture, which takes 48 to 72 hours to complete. Influenza is highly contagious and has been the etiology of numerous epidemics and pandemics. Identification of outbreaks is important so that isolation measures may be undertaken to control the spread of disease. Antiviral treatment can be effective if instituted early in the course of the disease. Therefore, rapid identification of influenza virus is important in making treatment decisions for high-risk patients and in instituting infection-control practices.

### ***Legionella pneumophila***

*Legionella pneumophila* is among the most common microbial etiologies of community-acquired pneumonia. Laboratory diagnosis depends on culture, direct fluorescent antibody tests, urinary antigens, or DNA probe. DNA probe techniques have also been used in epidemiologic investigations to identify the source of a *Legionella* outbreak.

### ***Mycobacteria Species***

Although mycobacterium can be directly identified in sputum samples (ie, acid-fast bacilli), these organisms may take 9 to 16 days to culture. DNA probes have also been used to identify specific mycobacterial groups (ie, mycobacterial tuberculosis, avian complex, intracellulare) after culture. Also, amplification techniques for *Mycobacterium tuberculosis* may be used in patients who have a positive smear. The rapid identification of *M. tuberculosis* permits prompt isolation of the patient and identification of the patient's contacts for further testing.

### ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is an atypical bacterium that is a common cause of pneumonia. It is most prevalent in younger patients below age 40 years and in individuals who live or work in crowded areas such as schools or medical facilities. The infection is generally responsive to antibiotics of the macrolide or quinolone class. Most patients with *M. pneumoniae* recover completely, although the course is sometimes prolonged for up to 4 weeks or more. Extrapulmonary complications of *M. pneumoniae* occur uncommonly, including hemolytic anemia and the rash of erythema multiforme.

### ***Neisseria gonorrhoeae***

Isolation by culture is the conventional form of diagnosis for this common pathogen, but culture requires specific sampling and plating techniques. Direct DNA probes and amplification techniques have also been used. *Neisseria* is often tested for at the same time as chlamydia.

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### **Papillomavirus**

*Papillomavirus* species are common pathogens that produce epithelial tumors of the skin and mucous membranes, most prominently the genital tract. Physical examination is the first diagnostic technique. Direct probe and amplification procedures have been actively investigated in the setting of cervical lesions. The ViraPap test is an example of a commercially available direct probe technique for identifying papillomavirus. There has been interest in evaluating the use of viral load tests of human papillomavirus to identify patients at highest risk of progressing to invasive cervical carcinoma.

### **Streptococcus, Group A**

Also referred to as *Streptococcus pyogenes*, this pathogen is the most frequent cause of acute bacterial pharyngitis. It can also give rise to a variety of cutaneous and systemic conditions, including rheumatic fever and post-streptococcal glomerulonephritis. A throat culture is the preferred method for diagnosing streptococcal pharyngitis. Also, a variety of commercial kits are now available that use antibodies for the rapid detection of group A carbohydrate antigen directly from throat swabs. While very specific, these kits are less sensitive than throat cultures so that a negative test may require confirmation from a subsequent throat culture. DNA probes have also been used for direct identification of streptococcus and can be used as an alternative to a throat culture as a back-up test to a rapid, office-based strep test.

### **Streptococcus, Group B**

Also referred to as *Streptococcus agalactiae*, group B streptococcus (GBS), is the most common cause of sepsis, meningitis, or death among newborns. Early-onset disease, within 7 days of birth, is related to exposure to GBS colonizing the mother's anogenital tract during birth. The Centers for Disease Control and Prevention have recommended either maternal risk assessment or screening for GBS in the perinatal period. Screening consists of obtaining vaginal and anal specimens for culture at 35 to 37 weeks of gestation. The conventional culture and identification process requires 48 hours. Therefore there has been great interest in developing rapid assays using DNA probes to shorten the screening process so that screening could be performed in the intrapartum period with the institution of antibiotics during labor.

### **Trichomonas vaginalis**

*Trichomonas* is a single-cell protozoan that is a common cause of vaginitis. The organism is sexually transmitted and can infect the urethra or vagina. The most common way of diagnosing *Trichomonas* is by clinical signs and by directly visualizing the organism by microscopy in a wet prep vaginal smear. The culture of *Trichomonas* is limited by poor sensitivity. Treatment with metronidazole results in a high rate of eradication. The disease is usually self-limited without sequelae, although infection has been associated with premature birth and higher rates of HIV transmission, cervical cancer, and prostate cancer.

## **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

A list of current U.S. FDA–approved or cleared nucleic acid–based microbial tests is available online. Table 1 lists tests approved or cleared by the FDA that do not have specific CPT codes.

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**Table 1. FDA-Approved/Cleared Tests Without CPT Codes**

FDA-Approved/Cleared Diagnostic Test	Test Type
<i>Bacillus anthracis</i>	Real-time PCR
<i>Coxiella burnetii</i> (Q fever)	Real-time PCR
<i>Enterococcus faecalis</i>	PNA FISH
<i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>	PNA FISH
<i>Escherichia coli</i> and/or <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>	PNA FISH
<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , and <i>Pseudomonas aeruginosa</i>	PNA FISH
<i>Francisella tularensis</i>	Real-time PCR
<i>Leishmania</i>	Real-time PCR
<i>Yersinia pestis</i>	Real-time PCR
Adenovirus	Multiplex real-time RT-PCR
Avian flu	Real-time RT-PCR
Human <i>metapneumovirus</i>	Multiplex real-time RT-PCR
Influenza virus A/H5	Real-time RT-PCR
Influenza virus H1N1	Real-time RT-PCR
Dengue virus	Real-time RT-PCR
Gram-positive/gram-negative bacteria panel	Multiplex nucleic acid amplification

FDA: U.S. FDA; FISH: fluorescence in situ hybridization; PCR: polymerase chain reaction; PNA: peptide nucleic acid; RT: reverse transcriptase.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose.

For some 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. For example, for group A *Streptococcus*, use of nucleic acid-based testing can result in a reduction in antibiotic use as a result of not needing to initiate empirical antibiotics pending culture results.

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### **NUCLEIC ACID PROBES**

#### **Clinical Context and Test Purpose**

Nucleic acid probes are used to identify a wide variety of microorganisms and to inform decisions about appropriate treatment for infection.

The question addressed in this evidence review is: Does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with various infections?

The following PICOTS were used to select literature to inform this review.

#### ***Patients***

The relevant population of interest is individuals with various infections or suspected infection.

#### ***Interventions***

The availability of nucleic acid probes has permitted the rapid direct identification of microorganisms' DNA or RNA. Amplification techniques result in exponential increases in copy numbers of a targeted strand of microorganism-specific DNA. The most commonly 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), which serves as a prognostic factor.

The direct probe technique, amplified probe technique, and probe with quantification methods vary regarding 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.

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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.

For reference, examples of some commercially available probe methods are outlined in Table 2.

**Table 2. Example Probe Methods**

Probe Method	Sample Commercially Available Products	Microorganism(s)
Direct probe	BD Affirm™ VPIII Microbial Identification System (Becton, Dickinson, Franklin Lakes, NJ) GasDirect (Hologic, Bedford, MA)	<i>Candida</i> , <i>Gardnerella</i> , <i>Trichomonas</i> species Group A <i>Streptococcus</i>
Amplified probe	Amplified MTD test (Hologic, Bedford, MA)	<i>Mycobacterium tuberculosis</i>
Probe with quantification	Cobas® Amplicor HIV-1 Monitor Test (Roche Molecular Diagnostics, Pleasanton, CA)	Human immunodeficiency virus-1

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.

### Comparators

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.

### Outcomes

The outcomes of interest are an improvement in symptoms and resolution of disease.

- 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

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Policy # 00488

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- organisms (eg, HIV), fastidious or lengthy culture requirements (eg, *Mycobacteria*, *Chlamydia*, *Neisseria* species), or difficulty in collecting an appropriate sample (eg, herpes simplex encephalitis).
- There is no way to definitively make a diagnosis without nucleic acid testing.
- The use of nucleic acid probe testing provides qualitatively different information than that available from standard cultures, such as information regarding disease prognosis or response to treatment. These include cases where quantification of viral load provides prognostic information or is used to measure response to therapy.

### **Timing**

Nucleic acid probes offer rapid detection; therefore, the timing of outcomes of interest is days following testing.

### **Setting**

Patients may present with signs and symptoms of potential infections in primary care or emergency care.

### **Technically Reliable**

Although nucleic acid probe technologies offer the potential for rapid, sensitive detection for a variety of microorganisms, there are technical and clinical considerations that should be accounted for in evaluating the technologies. They include:

- Lack of standardization in primers. For some microorganisms, the specific short segments of complementary DNA (probes or primers) used to initiate DNA replication are not commercially available, and different reference laboratories may use different products.
- Risk of cross-specimen contamination.
- Risk of nonspecific amplification, particularly if probes lack specificity.
- Challenges in clinical interpretation of results. Amplification of organisms representing latent infection or colonization cannot be distinguished from active, clinically significant infections. Also, amplification techniques may amplify fragments of nucleic acids, representing dead microorganisms, thus further clouding the clinical interpretation.

For any test, it is important to establish its analytic validity—the ability of the test to measure accurately and reliably the characteristic of interest for which the test was designed to identify or measure. Assessment of analytic validity focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this review. We focus on the clinical validity and clinical utility.

### **Clinically Valid and Clinically Useful**

#### ***Bartonella henselae* or *quintana***

Microbiologic detection of *Bartonella henselae* or *quintana* is difficult. A monoclonal antibody (mAb) to *B. henselae* has become commercially available, along with several types of PCR testing.

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A single-step PCR-based assay, which amplifies a fragment of the 16S-23S ribosomal RNA (rRNA) intergenic region conserved in *Bartonella* species, had 80% and 100% sensitivity in feline samples with 10 to 30 colony-forming unit per milliliter of bacteria and greater than 50 colony-forming unit per milliliter of bacteria, respectively. An earlier study (2000) demonstrated high sensitivity of a PCR-based assay for the *Bartonella* riboflavin synthase gene in bacterial samples and samples from feline samples and human lymph node samples. Another study (1999) reported high sensitivity of a PCR-based enzyme immunoassay in human lymph node samples.

In 2005, Hansmann et al reported on the diagnostic value of a PCR test for the *B. henselae* *htrA* gene in lymph node biopsy specimens or cytopunctures from 70 patients with suspected cat-scratch disease. Twenty-nine patients were considered to have definite cat-scratch disease based on clinical criteria; 16 were considered to have possible cat-scratch disease, and 26 subjects had an alternative diagnosis and served as controls. PCR analysis had a specificity of 100%. In patients with definite cat-scratch disease, PCR testing was positive for 76% (95% confidence interval [CI], 56.5% to 89.7%); in those with possible cat-scratch disease, PCR testing was positive in 20% (95% CI, 4.3% to 48.1%).

A 2009 study by Caponetti et al compared immunohistochemical analysis (IHC) for diagnosing *B. henselae* on surgical specimens with PCR detection and serologic testing. The study included 24 formalin-fixed, paraffin-embedded cases of lymphadenitis with histologic and/or clinical suspicion of *B. henselae*. Control cases included 14 cases of lymphadenopathy. The formalin-fixed, paraffin-embedded tissue sections were evaluated with a mAb to *B. henselae*, Steiner silver stain, and PCR that targeted *B. henselae* and *B. quintana*. Positive cases were as follows: Steiner silver stain, 11 (46%); PCR, 9 (38%); and IHC, 6 (25%). Only 2 (8%) cases were positive for all 3 techniques. All control cases were negative for IHC and PCR. The diagnostic sensitivity of these 3 tests is low for bartonellae. Steiner silver stain seems to be the most sensitive test but is the least specific. PCR is more sensitive than IHC and may, therefore, serve as a helpful second-line test on all IHC negative cases.

*B. henselae* infections can cause a wide range of symptoms, from self-limited regional lymphadenopathy to disseminated infection involving visceral organs, the central nervous system, or the heart. *B. henselae* may also present with fever of unknown origin. Antibiotic therapy is not always needed for uncomplicated infections, but it is required for severe or systemic infections. In cases where *B. henselae* is suspected, and treatment will change as a result of a positive test, the use of *Bartonella* PCR testing has the potential for clinical utility.

### **Candida Species**

*Candida* infections are most commonly caused by *Candida albicans*, but other species may be responsible. In complicated or severe cases (eg, candidemia and invasive focal infections) or compromised patients, it may be necessary to identify the infecting *Candida* species for appropriate treatment planning. DNA probes are available to aid in the diagnosis of possible *Candida* species infections. Amplified peptide nucleic acid tests have demonstrated high sensitivity and specificity levels of up to 100%. Some tests have been able to detect up to 6 *Candida* species. A rt-PCR assay, developed for the detection of the most common

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pathogenic *Candida* species using a single-reaction PCR assay targets a selected region of the 28S subunit of the fungal *rDNA* gene. In a 2012 study, the sensitivity and specificity of an assay based on quantitative real-time assay using duplex mutation primers were 100% and 97.4%, respectively. The data suggested that this assay might be appropriate for use in clinical laboratories as a simple, low-cost, and rapid screening test for the most frequently encountered *Candida* species.

Vulvovaginal candidiasis can typically be diagnosed by microscopy, and most cases are caused by *C. albicans*. Other species, such as *Candida glabrata*, may be responsible but are less common and may be difficult to detect by microscopy. Therefore, identification of *Candida* subspecies is not usually necessary and should be limited to use in complicated, recurrent or persistent cases that are resistant to azole/antifungal treatment. Additionally, symptomatic patients with negative microscopy may warrant subspecies testing.

### ***Chlamydomphila pneumoniae* or *Chlamydia trachomatis***

Probes are commercially available for the detection of *Chlamydomphila pneumoniae* or *Chlamydia trachomatis*. A study by Stanek et al (2012) demonstrated a *Chlamydia*-specific rt-PCR that targeted the conserved 16S *rRNA* gene. The test can detect at least 5 DNA copies and shows very high specificity without cross-amplification from other bacterial DNA. The PCR was validated with 128 clinical samples positive or negative for *C. trachomatis* or *C. pneumoniae*. Of 65 positive samples, 61 (93.8%) were found to be positive with the new PCR. Another 2012 study demonstrated the VERSANT CT/GC DNA 1.0 Assay performed with 99.2% specificity for *C. trachomatis* detection and 100% sensitivity.

For *C. trachomatis*, microbial culture is technically difficult, and nucleic acid amplification tests for *C. trachomatis* are generally preferred over other diagnostic methods, including direct fluorescent antibody tests, enzyme immunoassays, and nucleic acid hybridization tests. Diagnosis of *C. trachomatis* has clinical utility in a variety of settings. Treatment of individuals with *C. trachomatis* genital infection prevents sexual transmission and complications, including pelvic inflammatory disease. Treatment of pregnant women will prevent the transmission of infection to infants during delivery. Antibiotic treatment is indicated in neonatal conjunctivitis caused by *C. trachomatis*.

PCR-based tests specific for *C. pneumoniae* have been described in the investigational setting. Gaydos et al (1994) compared with tissue culture, PCR enzyme immunosorbent assay, direct fluorescent antibody stain, and serology for the diagnosis of *C. pneumoniae* in 56 patients with respiratory symptoms and 80 asymptomatic individuals. Determining test characteristics is limited by the lack of a true criterion standard, given the difficulty in culturing *C. pneumoniae*. However, when culture- and/or direct fluorescent antibody-positive results were used as a reference, PCR had a sensitivity and specificity of 76.5% and 99.0%, respectively. However, the use of PCR-based tests for *C. pneumoniae* in clinical practice has not been well defined.

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### *Section Summary: Chlamydomphila pneumoniae or Chlamydia trachomatis*

The evidence for the clinical validity or clinical utility of *C. pneumoniae* probes is limited. One study reported high sensitivity and specificity for a PCR-based test but the study was small (N=56). The clinical implications of testing for *C. pneumoniae* are unclear.

Nucleic acid amplification tests for *C. trachomatis* are generally the preferred diagnostic method. The tests have clinical utility in that treatment of infection prevents sexual transmission and complications to partners and maternal transmission of infection to infants during delivery.

### ***Clostridium difficile***

DNA probes for *Clostridium difficile* using PCR have been commercially available since 2009. Eastwood et al (2009) compared the performance characteristics of numerous DNA probes with cytotoxic assays and cultures. The results demonstrated a mean sensitivity of 82.8% (range, 66.7%-91.7%) and a mean specificity of 95.4% (range, 90.9%-98.8%).

Rapid identification of *C. difficile* allows for early treatment of the disease and timely institution of isolation measures to reduce transmission. Because of the advantages of early identification of *C. difficile*, the use of PCR-based testing for *C. difficile* has potential to improve health outcomes.

### ***Central Nervous System Bacterial and Viral Panel***

The standard approach to the diagnosis of meningitis and encephalitis is culture and pathogen-specific PCR testing of cerebrospinal fluid (CSF) based on clinical characteristics. These techniques have a slow turnaround time, which can delay administration of effective therapies and lead to unnecessary empirical administration of broad-spectrum antimicrobials.

The FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics, Salt Lake City, UT) is a nucleic acid-based test that simultaneously detects multiple bacterial, viral, and yeast nucleic acids from CSF specimens obtained via lumbar puncture from patients with signs and/or symptoms of meningitis and/or encephalitis. The test has been cleared for marketing through the U.S. FDA 510(k) process. The test identifies 14 common organisms responsible for community-acquired meningitis or encephalitis:

Bacteria: *Escherichia coli* K1; *Haemophilus influenzae*; *Listeria monocytogenes*; *Neisseria meningitidis*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*;  
Viruses: Cytomegalovirus; *Enterovirus*; *Herpes simplex virus 1*; *Herpes simplex virus 2*; Human herpesvirus 6; *Human parechovirus*; *Varicella zoster virus*;  
Yeast: *Cryptococcus neoformans/gattii*.

Run-time is approximately 1 hour per specimen.

The clinical validity of the test has been analyzed using 1560 CSF specimens collected at 11 U.S. sites and several smaller studies. The following study selection criteria were used to assess whether the central nervous system panel is clinically valid: (1) eligibility and selection are described, and the study population represents the population of interest; (2) the test is compared with a credible reference standard; (3) studies

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report sensitivity, specificity, and preferably predictive values; studies that completely report true- and false-positive results are ideal. Several studies failed to meet selection criteria. The study characteristics and results of selected studies are shown in Tables 3 and 4.

In the largest study (Leber et al, 2016), 1560 samples were tested. The samples were from children and adults with available CSF but not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis. Even the most prevalent organisms were present only a small number of times in the samples. The specificities ranged from 98% to 100% and, given the high number of true negatives, the specificities were estimated with tight precision. However, given the small number of true positives, the sensitivities to detect any given organism could not be estimated with precision. A total of 141 pathogens were detected in 136 samples with the FilmArray and 104 pathogens detected using comparator methods; 43 FilmArray results were “false-positive” compared with the comparator method and six were “false-negative.” For 21 of the 43 “false-positives,” repeat testing of the FilmArray, comparator, or additional molecular testing supported the FilmArray results. The remaining 22 “false-positives” (16% of all positives) were unresolved. Codetections were observed in 3.7% (5/136) positive specimens. All five included a bacterial and viral positive result, and all 5 specimens were found to have a false-positive result demonstrated by comparator testing. The investigators suggested that the discrepancies could have been due to specimen contamination or another problem with the assay configuration or testing process.

The smaller studies were consistent with Leber (2016) in estimating the specificities for all included pathogens to be greater than 98%. However, there were also a very low number of true positives for most pathogens in these studies and thus the estimates of sensitivities were imprecise. Relevance, study design, and trial conduct gaps are shown in Tables 5 and 6.

**Table 3. Study Characteristics of Clinical Validity Studies of CNS Panel**

Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Leber et al (2016)	Children and adults from whom a CSF specimen was available from standard care testing for bacterial culture; not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis	Nonconcurrent prospective	Culture and PCR	Processed within 7 d of collection or immediately frozen for future testing	Yes
Hanson et al (2016)	Children and adults from whom a CSF specimen was available who had been tested with at least 1 conventional method	Retrospective, selection method not clear	Culture and PCR with discrepancy resolution LDT PCR	Stored up to 2 y after collection	Yes
Graf et al (2017)	Positive samples (children) selected based on positivity of reference method for any of	Retrospective, convenience	Culture and PCR	Stored up to 2 y after collection	NR

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Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
	targets on the CNS panel. Negative samples selected based on negativity of reference sample and with preference for samples highly suggestive of meningitis or encephalitis				

CNS: central nervous system; CSF: cerebrospinal fluid; LDT: laboratory-developed test; NR: not reported; PCR: polymerase chain reaction.

**Table 4. Results of Clinical Validity Studies of CNS Panel**

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/Positive % Agreement	Specificity/Negative % Agreement
<b>Leber et al (2016)</b>	1643	1560	Insufficient volume, outside the 7-d window, repeat subject, or invalid FilmArray test.			
Bacteria						
<i>Escherichia coli K1</i>				0.1	100 (34 to 100)	99.9 (99.6 to 100)
<i>Haemophilus influenzae</i>				0.06	100 (NA)	99.9 (99.6 to 100)
<i>Listeria monocytogenes</i>				0		100 (99.8 to 100)
<i>Neisseria meningitides</i>				0		100 (99.8 to 100)
<i>Streptococcus agalactiae</i>				0.06	0 (NA)	99.9 (99.6 to 100)
<i>Streptococcus pneumoniae</i>				0.3	100 (51 to 100)	99.2 (98.7 to 99.6)
Viruses						
Cytomegalovirus				0.2	100 (44 to 100)	99.8 (99.4 to 99.9)
Enterovirus				2.9	96 (86 to 99)	99.5 (99.0 to 99.8)
Herpes simplex virus 1				0.1	100 (34 to 100)	99.9 (99.5 to 100)
Herpes simplex virus 2				0.6	100 (72 to 100)	99.9 (99.5 to 100)
Human herpesvirus 6				1.3	86 (65 to 95)	99.7 (99.3 to 99.9)
Human parechovirus				0.6	100 (70 to 100)	99.8 (99.4 to 99.9)
Varicella zoster virus				0.3	100 (51 to 100)	99.8 (99.4 to 99.9)
Yeast						
<i>Cryptococcus neoformans/ Cryptococcus gattii</i>				0.06	100 (NA)	99.7 (99.3 to 99.9)
<b>Hanson et al (2016)</b>	342	342		NR		
Bacteria						
<i>Escherichia coli K1</i>			0.3	100 (3 to 100)	100 (98 to 100)	
<i>Haemophilus influenzae</i>			1.5	100 (48 to 100)	100 (97 to 100)	
<i>Listeria monocytogenes</i>			0	NA	100 (98 to 100)	
<i>Neisseria meningitides</i>			0.3	100 (3 to 100)	100 (98 to 100)	

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Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
<i>Streptococcus agalactiae</i>				0.9	67 (9 to 99)	99 (95 to 100)
<i>Streptococcus pneumoniae</i>				1.5	100 (48 to 100)	99 (96 to 100)
Viruses						
Cytomegalovirus				2.0	57 (18 to 90)	100 (91 to 100)
Enterovirus				11.1	97 (86 to 100)	100 (69 to 100)
Herpes simplex virus 1				3.5	93 (66 to 100)	98 (89 to 100)
Herpes simplex virus 2				8.5	100 (88 to 100)	100 (82 to 100)
Human herpesvirus 6				5.6	95 (74 to 100)	100 (93 to 100)
Human parechovirus				0.3	100 (3 to 100)	100 (93 to 100)
Varicella zoster virus				9.4	100 (89 to 100)	100 (79 to 100)
Yeast						
<i>Cryptococcus neoformans/ Cryptococcus gattii</i>				2.6	64 (35 to 87)	NA
<b>Graf et al (2017)</b>	133	133	NR			
Bacteria						
<i>Haemophilus influenzae</i>				NA <sup>a</sup>	100 (1 to 100) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
<i>Streptococcus agalactiae</i>				NA <sup>a</sup>	100 (1 to 100) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
<i>Streptococcus pneumoniae</i>				NA <sup>a</sup>	100 (28 to 100) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
Viruses						
Enterovirus				NA <sup>a</sup>	95 (82 to 99) <sup>b</sup>	100 (94 to 100) <sup>b</sup>
Herpes simplex virus 1				NA <sup>a</sup>	50 (7 to 93) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
Herpes simplex virus 2				NA <sup>a</sup>	100 (1 to 100) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
Human herpesvirus 6				NA <sup>a</sup>	100 (9 to 100) <sup>b</sup>	100 (96 to 100) <sup>b</sup>
Human parechovirus				NA <sup>a</sup>	94 (70 to 100) <sup>b</sup>	100 (95 to 100) <sup>b</sup>

CI: confidence interval; NA: not available; NR: not reported.

<sup>a</sup> Positives and negatives retrospectively selected from a convenience sample with different selection criteria; prevalence is unknown.

<sup>b</sup> Confidence intervals not provided in publication; estimated based on available information.

**Table 5. Relevance Gaps of Studies of CNS Panel**

Study	Population	Intervention	Comparator	Outcomes	Duration of Follow-Up
Leber et al (2016)	4. Participants not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis	3. Used investigational version of test but varies from marketed version only in that Epstein-Barr virus is not available in the marketed version			
Hanson et al (2016)	3. Selection criteria with respect to clinical	3. Used investigational version (see			

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	characteristics not described	above)			
Graf et al (2017)	4. Selection criteria varied for positive and negative samples				
<b>Key</b>	<ol style="list-style-type: none"> <li>1. Intended use population unclear</li> <li>2. Clinical context for test is unclear</li> <li>3. Study population unclear</li> <li>4. Study population not representative of intended clinical use</li> <li>5. Study population is subpopulation of intended use</li> </ol>	<ol style="list-style-type: none"> <li>1. Classification thresholds not defined</li> <li>2. Version used unclear</li> <li>3. Not version currently in clinical use</li> </ol>	<ol style="list-style-type: none"> <li>1. Classification thresholds not defined</li> <li>2. Not compared with credible reference standard</li> <li>3. Not compared with other tests in use for same purpose</li> </ol>	<ol style="list-style-type: none"> <li>1. Study does not directly assess a key health outcome</li> <li>2. Evidence chain or decision model not explicated</li> <li>3. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)</li> <li>4. Reclassification of diagnostic or risk categories not reported</li> <li>5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)</li> </ol>	<ol style="list-style-type: none"> <li>1. Follow-up duration not sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determined)</li> </ol>

FN: false-negative; FP: false-positive; TN: true negative; TP: true positive.

**Table 6. Study Design and Conduct Gaps**

Study	Selection	Blinding	Delivery of Test	Selective Reporting	Completeness of Follow-Up	Statistical
Leber et al (2016)			2. Many tests performed on frozen samples			
Hanson et al (2016)	1. Not clear if participants were consecutive		2. Many tests performed on frozen samples		1. Not clear if there were indeterminate samples	
Graf et al (2017)	3. Selection not random or consecutive and varied for positive and negatives	1. Not clear if blinded	2. Many tests performed on frozen samples		1. Not clear if there were indeterminate samples	1. Confidence intervals not provided
<b>Key</b>	1. Selection not	1. Not blinded to results	1. Timing of delivery of	1. Not registered	1. Inadequate description of	1. Confidence intervals

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Study	Selection	Blinding	Delivery of Test	Selective Reporting	Completeness of Follow-Up	Statistical
	described 2. Selection not random nor consecutive (ie, convenience )	of reference or other comparator tests	index or reference test not described 2. Timing of index and comparator tests not same 3. Procedure for interpreting tests not described 4. Expertise of evaluators not described	2. Evidence of selective reporting 3. Evidence of selective publication	indeterminate and missing samples 2. High number of samples excluded 3. High loss to follow-up or missing data	and/or p values not reported 2. No statistical test reported to compare with alternatives

### Section Summary: Central Nervous System Bacterial and Viral Panel

The FilmArray ME Panel provides fast diagnoses compared with standard culture and pathogen-specific PCR and, because it combines multiple individual nucleic acid tests, clinicians can test for several potential pathogens simultaneously. The test uses only a small amount of CSF, leaving remaining fluid for additional testing if needed. The test is highly specific for the included organisms. However, due to the low prevalence of these pathogens overall, the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest study were reported to be false-positives, which could cause harm if used to make clinical decisions. Also, a negative panel result does not exclude infection due to pathogens not included in the panel.

### Cytomegalovirus

Diagnosis of CMV can be made by culture and/or serologies. However, CMV culture for establishing a diagnosis is limited by the slow growth of CMV and low sensitivity. Serologies provide indirect evidence of current and/or historical infection. A variety of tests to detect CMV DNA have been developed, including but not limited to Hybrid Capture (Digene Corp.), Amplicor CMV Monitor Tests (Roche Molecular Diagnostics), and TaqMan. The specific techniques used may vary by local availability, but studies have suggested that all provide complementary information.

Clinically, molecular assays for CMV are primarily used to quantify CMV viral load, particularly to identify asymptomatic immunosuppressed patients (ie, transplant recipients) who would be candidates for preemptive antiviral therapy. For example, among transplant recipients, CMV infections account for about two-thirds of deaths in the immediate posttransplant period (ie, up to 50 days posttransplant), and thus, a variety of preventive therapies have been investigated. One strategy proposes that all at-risk patients (ie,

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seropositive patients, or seronegative patients receiving a seropositive organ) be treated prophylactically with antiviral therapy during the first 100 days after transplantation. While this strategy has been shown to be effective in reducing the risk of CMV disease, it results in a large number of patients being treated unnecessarily. Therefore, preemptive therapy has become an accepted option, in which antiviral therapy is initiated when a laboratory technique identifies an increasing viral load. Late CMV disease, defined as occurring after 100 days, is also a concern, and viral loads can also be monitored to prompt antiviral therapy.

### **Enterovirus**

Amplified DNA probes are available for detecting this group of viruses including the polioviruses, coxsackieviruses, echoviruses, and other enteroviruses. In addition to 3 polioviruses, there are more than 60 types of non-polio enteroviruses that can cause disease in humans. Several FDA-approved test kits are available including the GeneXpert Enterovirus Assay, with sensitivity, specificity, PPV, and NPV of 82.1%, 100%, 100%, and 96.2%, respectively. In this study, molecular assays were superior to viral culture for detecting enterovirus RNA in CSF. GeneXpert Enterovirus Assay showed a high specificity but a lower sensitivity for the detection of enterovirus RNA compared with the reverse transcriptase qPCR assay. In at least some clinical situations, the yield of virus identification with PCR has been shown to be higher than with viral culture (eg, suspected pediatric enteroviral encephalomyelitis).

Enteroviruses are associated with a wide spectrum of clinical symptoms, including exanthematous/ enanthematous syndromes (eg, hand-foot-and-mouth disease, herpangina), viral meningitis and encephalitis, acute paralysis, and myocarditis. In neonates, enteroviruses can cause life-threatening systemic infections. In general, management is supportive and addresses symptoms. No antiviral medications are currently approved for the treatment of enterovirus infections. However, there are some situations in which PCR-based testing for enteroviruses allows for discontinuation of therapy for alternative diagnoses (eg, bacterial meningitis). For example, the use of enterovirus PCR testing has been associated with shorter hospital length of stay among febrile infants evaluated for serious bacterial infection with lumbar puncture. Similarly, an observational study (2015) reported that the use of enterovirus PCR testing is associated with reduced hospital stay and reduced antibiotic duration in adults with aseptic meningitis.

### **Vancomycin-Resistant Enterococcus**

Probes are available for detecting vancomycin resistance of organisms (eg, for *Enterococcus*). These probes can detect vancomycin resistance rapidly and accurately so that appropriate antibiotic selection can be made and infectious precautions, such as isolation, can be instituted.

### **Gardnerella vaginalis**

A 2006 study evaluated vaginal specimens from 321 symptomatic women analyzed for bacterial vaginosis, using both Gram stain with Nugent criteria and a DNA hybridization test (Affirm VPIII hybridization test). Of the 321 patients, 115 (35.8%) were Gram-positive for bacterial vaginosis, and 126 (39.2%) were negative. A total of 80 (25.0%) patients demonstrated intermediate Gram staining that was also considered negative. The DNA hybridization test detected *Gardnerella vaginalis* in 107 (93.0%) of 115 vaginal specimens positive

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for bacterial vaginosis diagnosed by Gram stain. Compared with the Gram stain, the DNA hybridization test had a sensitivity of 87.7% and a specificity of 96.0%. PPVs and NPVs of the DNA hybridization test were 93.0% and 92.7%, respectively. The study concluded the Affirm VPIII hybridization test correlated well with Gram stain and may be used as a rapid diagnostic tool to exclude bacterial vaginosis in women with genital complaints.

### **Gastrointestinal Pathogen Panel**

Infectious gastroenteritis may be caused by a broad spectrum of pathogens resulting in the primary symptom of diarrhea. Panels for gastrointestinal pathogens use multiplex amplified probe techniques and multiplex reverse transcription for the simultaneous detection of many gastrointestinal pathogens such as *C. difficile*, *Escherichia coli*, *Salmonella*, *Shigella*, norovirus, rotavirus, and *Giardia*. Several studies of gastrointestinal pathogen panels have demonstrated overall high sensitivities and specificities and indicated the panels might be useful for detecting causative agents for gastrointestinal infections. Studies have suggested that panels limited to bacterial pathogens have similarly high sensitivities and specificities compared with bacterial culture. Beckmann et al (2014) reported findings on the use of a commercially available gastrointestinal pathogen panel (Luminex Molecular Diagnostics, Toronto, ON) in a group of 120 pediatric patients with suspected viral gastroenteritis and a group of 151 adult and 25 pediatric patients (n=176) returning from the tropics with gastrointestinal symptoms. Positive results were detected in 21 samples from adults (11% of 185 samples) and in 66 pediatric samples (52% of samples).

Other studies have evaluated panels for bacteria associated with hemorrhagic diarrhea (*Salmonella* species, *Shigella* species, enterohemorrhagic *E. coli*, and *Campylobacter* species) and have reported high sensitivities and specificities. Other panels are comprised of only viral infectious gastroenteritis pathogens. The yield of testing is likely to vary based on panel composition.

Access to a rapid method for etiologic diagnosis of gastrointestinal infections may lead to more effective early treatment and infection-control measures. However, in most instances, when there is suspicion for a specific pathogen, individual tests could be ordered. There may be a subset of patients with an unusual presentation who would warrant testing for a panel of pathogens at once, but that subset has not been well defined.

### **Hepatitis B**

Hepatitis B genotyping has been used to predict response to various antiviral agents. Also, the viral load is used to determine which patients with hepatitis B are candidates for antiviral therapy. Guidelines from the National Institutes of Health (2009) and the American Association for the Study of Liver Diseases (2009) have included quantitative hepatitis B DNA levels in the diagnostic criteria for chronic and resolved hepatitis B and inactive hepatitis B carrier states.

### **Hepatitis C**

Diagnostic tests for hepatitis C can be divided into 2 general categories: (1) serologic assays that detect antibody to hepatitis C virus (anti-HCV); and (2) molecular assays that detect, quantify, and/or characterize

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HCV RNA genomes within an infected patient. Detection of HCV RNA in patient specimens by PCR provides evidence of active HCV infection and is used to confirm the diagnosis and monitor the response to antiviral therapy. The use of direct-acting antiviral agents (with or without interferon) has the potential to treat and cure chronic hepatitis C. Therapy-induced sustained virologic remission has been shown to reduce liver-related death, liver failure, and to a lesser extent, hepatocellular carcinoma.

### ***Hepatitis G***

It is possible that hepatitis C is part of a group of GB viruses, rather than just a single virus. It is unclear whether hepatitis G causes a type of acute or chronic illness. When diagnosed, acute hepatitis G infection has usually been mild and brief, and there is no evidence of serious complications, but it is possible that, like other hepatitis viruses, it can cause severe liver damage resulting in liver failure. The only method of detecting hepatitis G is by rt-PCR and direct sequencing for 4 randomly selected samples followed by phylogenetic analysis.

### ***Herpes Simplex Virus***

Typing of HSV isolates is required to identify the virus isolated in culture. The methods available for this include antigen detection by immunofluorescence (IF) assays and PCR. A 2009 cross-sectional study used 4 reference strains and 42 HSV isolates obtained from patients between September 1998 and September 2004. These isolates were subjected to testing using a MAb-based IF test and a PCR that detects the polymerase (pol) gene of HSV isolates. The observed agreement of the MAb IF assay with the PCR was 95.7%. A total of 54.8% (23/42) of isolates tested by IF typing were found to be HSV-1, 40.5% (17/42) were HSV-2, and 2 (4.8%) were untypable using the MAb IF assay. The 2 untypable isolates were found to be HSV-2 using the pol PCR. According to the American Academy of Family Physicians, antiviral medications have expanded treatment options for the 2 most common cutaneous manifestations, HSV-1 and HSV-2. Acyclovir therapy remains an effective option; however, famciclovir and valacyclovir offer improved oral bioavailability and convenient oral dosing schedules but at a higher cost. Patients who have 6 or more recurrences of genital herpes per year can be treated with daily regimens, which are effective in suppressing 70% to 80% of symptomatic recurrences.

### ***Human Herpesvirus 6***

HHV-6 can be detected with a number of immunoassays. The high rate of seropositivity in the general population makes interpreting positive results difficult. Historically, paired samples with a rise in antibody titer have been needed to diagnose an active infection.

Qualitative and quantitative PCR tests are available for HHV-6 in blood and other samples. At least 1 evaluation (2014) of rt-PCR detecting viral mRNA transcripts in hematopoietic cell transplant subjects showed good analytic validity.

Most often, in healthy patients, HHV-6 causes no symptoms or a mild-self-limited illness. In these cases, a definitive diagnosis of HHV-6 has little utility. However, the primary HHV-6 infection can cause severe disease including thrombocytopenia, hepatitis, myocarditis, and meningoencephalitis. In

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immunosuppressed patients, particularly hematopoietic cell transplant recipients, HHV-6 reactivation may cause a range of severe symptoms. A number of antiviral agents are active against HHV-6 (eg, ganciclovir, foscarnet). A variety of treatment strategies are used for immunosuppressed patients, which can be classified as prophylactic (all at-risk patients treated), preemptive (patients treated when viral replication is detected), and curative (patients treated when the disease is confirmed). The use of a quantitative HHV-6 assay may be used in treatment-related decisions.

### ***Human Immunodeficiency Virus 1***

Validated DNA probes are widely available for diagnosis and human immunodeficiency virus 1 (HIV-1) quantification. Quantification is standard of care to determine viral load in infected patients to monitor response to antiretroviral therapies.

### ***Human Immunodeficiency Virus 2***

DNA probes are available for diagnosis and quantification of HIV-2. HIV-2 is most commonly found in Western Africa, although it has been reported in the United States. Blood donations are routinely tested for HIV-2, but clinical testing for HIV-2 is typically limited to those in contact with persons in a country where HIV-2 is endemic or when clinical evaluation suggests HIV infection, but testing for Human Immunodeficiency Virus 1 is negative. HIV-2 quantification is regularly done to determine viral load in infected patients to monitor response to antiretroviral therapies.

### ***Human Papillomavirus***

There has been research into the relation between human papilloma viral load and progression of low-grade cervical lesions to cervical cancer. While studies have reported that high-grade lesions are associated with higher viral loads, clinical utility is based on whether the presence of increasing viral loads associated with low-grade lesions is associated with disease progression. For example, current management of cervical smears with “atypical cells of uncertain significance” suggests testing with human papillomavirus (HPV), and then, if positive, followed by colposcopy. It is hypothesized that colposcopy might be deferred if a low viral load was associated with a minimal risk. However, how treatment decisions may be tied to measurements of viral load is unclear. Persistent infection with various HPV genotypes has also been linked with cervical lesions and may influence treatment decisions. HPV genotypes 16 and 18 have been most associated with carcinogenesis. Patients with high-risk HPV genotypes may warrant direct referral to colposcopy.

### ***Influenza Virus***

Numerous different strains of influenza virus can be identified by DNA probes. Published studies have indicated the improved sensitivity of PCR for identifying influenza and distinguishing influenza from related viruses. Lassauniere et al (2010) used a multiplex, real-time reverse transcriptase PCR probe to identify 13 respiratory viruses, including influenza A and B. Screening of 270 samples that were negative on immunofluorescence assays revealed the presence of a respiratory virus in 44.1%. Probes have also been developed to identify specific strains of influenza associated with epidemics, such as the H1N1 influenza virus. Because of the importance of early identification of outbreaks for infection-control purposes and of

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initiating antiviral therapy early in the course of illness (if indicated), there is clinical utility for the use of these tests.

### ***Legionella pneumophila***

Typically, methods to detect *Legionella pneumophila*, which is associated with 90% of culture-confirmed *Legionella* species infections, have included culture, serology, and/or urine antigen testing, which are limited by relatively low sensitivities and long turnaround times.

DNA probes for *Legionella pneumophila* have been developed. A 2010 study compared the usefulness of 2 rt-PCR assays (qrt-PCR<sub>mip</sub> targeting *L. pneumophila* and qrt-PCR<sub>16S</sub> targeting all *Legionella* species) performed on lower respiratory tract samples for diagnostic and prognostic purposes in 311 patients hospitalized for community-acquired pneumonia. The Now Legionella urinary antigen test from Binax (Portland, ME) was used as a reference test. One subset of 255 community-acquired pneumonia patients admitted to a single hospital in 2005 and 2006 were evaluated, and the sensitivities, specificities, PPVs, and NPVs for both rt-PCR tests were 63.6%, 98.7%, 77.7%, and 97.4%, respectively. Diederer et al (2008) evaluated the use of a rt-PCR assay for *Legionella* species in 151 subjects with respiratory infections, 37 (25%) of whom fulfilled the European Working Group for Legionella Infections criteria for *Legionella* pneumonia and were considered to have *Legionella* pneumonia. For a 16S rRNA-based PCR, the estimated sensitivity and specificity were 86% (95% CI, 72% to 95%) and 95% (95% CI, 90% to 98%), respectively. For a *mip* gene-based PCR, the estimated sensitivity and specificity were 92% (95% CI, 78% to 98%) and 98% (95% CI, 93% to 100%), respectively. Another study (2012) reported a significantly higher sensitivity for PCR vs culture in detecting *L. pneumophila* in samples taken within 2 days or less of hospitalization (94.7% vs 79.6%, respectively) or 3 to 14 days of hospitalization (79.3% and 47.8%, respectively).

Delay in initiating appropriate antimicrobial therapy for Legionnaire's disease is associated with increased mortality, which makes a strong indirect argument for improved early detection with nucleic acid probes.

### ***Mycobacteria Species***

DNA probes are available to distinguish between *Mycobacterium* species. In a 2012 study, the extracted DNA specimens from *Mycobacterium* species and non-mycobacterial species were tested using peptide nucleic acid probe-based rt-PCR assay to evaluate potential cross-reactivity. A total of 531 respiratory specimens (482 sputum specimens, 49 bronchoalveolar washing fluid specimens) were collected from 230 patients in July and August 2011. All specimens were analyzed for *Mycobacteria* by direct smear examination, mycobacterial culture, and peptide nucleic acid probe-based rt-PCR assay. In cross-reactivity tests, no false-positive or false-negative results were evident. When the culture method was used as the criterion standard test for comparison, peptide nucleic acid probe-based rt-PCR assay for detection of *Mycobacterium tuberculosis* complex (MTBC) had a sensitivity and specificity of 96.7% (58/60) and 99.6% (469/471), respectively. Assuming the combination of culture and clinical diagnosis as the standard, the sensitivity and specificity of the rt-PCR assay for detection of MTBC were 90.6% (58/64) and 99.6%

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(465/467), respectively. The new rt-PCR for the detection of nontuberculous mycobacteria had a sensitivity and specificity of 69.0% (29/42) and 100% (489/489), respectively.

### ***Mycobacterium tuberculosis***

DNA probes are available to diagnose *M. tuberculosis* infection. In a 2012 study, an in-house IS6110 rt-PCR IH IS6110, MTB Q-PCR Alert (Q-PCR) and GenoType MTBDRplus (MTBDR) were compared for the direct detection of MTBC in 87 specimens. The samples included 82 first smear-positive specimens and 3 smear-negative specimens. The sensitivities of IH IS6110, Q-PCR, MTBDR, and IH ITS for MTBC detection were 100%, 92%, 87%, and 87% respectively, compared with culture. Both IS6110-based rt-PCRs (in-house and Q-PCR) were similar in performance with 91.2% concordant results for MTBC detection. However, none of the rt-PCR assays tested provide drug resistance data. Detection and drug resistance profiling is necessary for successful treatment of infection.

### ***Mycobacterium avium and Mycobacterium intracellulare***

DNA probes are available to diagnose *Mycobacterium avium* and *Mycobacterium intracellulare* infection. One 2011 study evaluated the performance of the GenoType Mycobacteria Direct test for rapid molecular detection and identification of the MTBC and 4 clinically important nontuberculous mycobacteria (*M. avium*, *M. intracellulare*, *M. kansasii*, *M. malmoense*) in smear-negative samples. A total of 1570 samples (1103 bronchial aspiration, 127 sputa, 340 extrapulmonary samples) were analyzed. When evaluated, the performance criteria in combination with a positive culture result and/or the clinical outcome of the patients, the overall sensitivity, specificity, PPVs, and NPVs were found to be 62.4%, 99.5%, 95.9%, and 93.9%, respectively, whereas they were 63.2%, 99.4%, 95.7%, and 92.8%, respectively, for pulmonary samples and 52.9%, 100%, 100%, and 97.6%, respectively, for extrapulmonary samples. Among the culture-positive samples which had *Mycobacterium* species detectable by the GenoType Mycobacteria Direct test, 3 samples were identified to be *M. intracellulare*, and one was identified to be *M. avium*. However, 5 *M. intracellulare* samples and an *M. kansasii* sample could not be identified by the molecular test and were found to be negative.

### ***Mycoplasma pneumoniae***

Probes for *Mycoplasma pneumoniae* have been developed. In a 2015 study using probes, a very high sensitivity and specificity for *M. pneumoniae* infection was reported (99.1% and 100%, respectively). Chalker et al (2011) tested 3987 nose and throat swabs from patients presenting with symptoms of a respiratory tract infection. *Mycoplasma* DNA was present in 1.7% of patients overall and was more common in children aged 5 to 14 years, in whom 6.0% of samples were positive. Probes have also been developed to test for mycoplasma strains with macrolide resistance. Peuchant et al (2009) found that 9.8% (5/51) of mycoplasma strains were macrolide resistant.

In many cases, management of *M. pneumoniae* infection does not require definitive diagnosis (eg, community-acquired pneumonia). However, there are some cases where *M. pneumoniae* is associated with severe illnesses that can have a variety of causes, in which definitive diagnosis may make a difference in treatment. *M. pneumoniae* PCR can be used to detect *M. pneumoniae* in patients with Stevens-Johnson

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syndrome and refractory/severe pneumonia. At least 1 study (2014) has suggested that inappropriate antibiotic use may worsen fulminant mycoplasma infection, and patients benefit from early administration of appropriate antimycoplasmal drugs with steroids.

### ***Neisseria gonorrhoeae***

Probes for *Neisseria gonorrhoeae* have been developed for commercial use. These probes are often a combination test with *C. trachomatis*. A 2012 study demonstrated that the PPV of the screening PCR (Cobas 4800 CT/NG PCR screening assay) in urine specimens remained high (98.75%) even though the prevalence of *gonorrhoeae* was low. Another 2012 study demonstrated the VERSANT CT/GC DNA 1.0 assay performed with a 99.4% and 99.2% of specificity for *N. gonorrhoeae* and *C. trachomatis* detection, respectively, whereas sensitivity was 100% for both *C. trachomatis* and *N. gonorrhoeae*. As a comparator, culture methods were 100% specific, but far less sensitive. As a clinical consideration, patients accept antibiotic treatment before their infection status has been confirmed.

### ***Respiratory Viral Panel***

A broad spectrum of pathogens is causative for respiratory tract infections, but symptoms are mostly similar. The identification of the causative viruses is only feasible using multiplex PCR or several monoplex PCR tests in parallel. Several studies of various respiratory viral panels have demonstrated the multiplex assay detected clinically important viral infections in a single genomic test and thus, may be useful for detecting causative agents for respiratory tract disorders. A 2011 randomized study by Brittain-Long et al, which assessed 406 patients with access to a rapid, multiplex PCR assay used to detect 13 viruses, reported lower antibiotic prescription rates (4.5% vs 12.3%, respectively) vs delayed identification with no significant difference in outcomes at follow-up ( $p=0.359$ ). Access to a rapid method for etiologic diagnosis of respiratory tract infections might reduce antibiotic prescription rates at the initial visit in an outpatient setting.

### ***Staphylococcus aureus and Methicillin-Resistant Staphylococcus aureus***

Probes are available for the detection of *Staphylococcus aureus*. These probes not only distinguish between coagulase-negative *Staphylococcus* and *S. aureus*, but they can also detect methicillin-resistant species with high accuracy. Given the importance of establishing an early and accurate diagnosis in clinical situations in which an *S. aureus* infection is likely, and there is a substantial likelihood of methicillin-resistant species, there is a clinical utility for testing in these situations.

### ***Streptococcus, Group A***

While group A *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) can cause a variety of clinical symptoms including impetigo, pharyngitis, and more invasive infections (eg, necrotizing fasciitis, pneumonia), most of the focus of rapid detection methods is on the diagnosis of GAS pharyngitis. Patients with confirmed acute GAS pharyngitis are typically treated with antibiotics, which shorten the duration of symptoms modestly and help prevent acute rheumatic fever. The diagnosis of GAS pharyngitis can be made by culture, which has a sensitivity of 90% to 95% but is limited by a slow turnaround time (1-2 days), which may hamper decisions about initiating antibiotic therapy. Point-of-care rapid antigen detection tests

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are widely used to diagnose GAS pharyngitis. Point-of-care rapid antigen detection tests are characterized by high specificity (~95%) but poor sensitivity (70%-90%) compared with culture.

Several nucleic acid probes that detect either unamplified or amplified nucleotides have been developed. Typically, these tests have a shorter turnaround time than culture, and some are intended to be used as point-of-care tests. Table 7 (though not meant to be all-inclusive) offers some examples of tests, with data provided on turnaround times, sensitivities and specificities, and other characteristics appearing on relevant package inserts.

**Table 7. Examples of Commercially Available Group A *Streptococcus* Probes**

Test	Manufacturer	Characteristics
Gen-Probe Group A <i>Streptococcus</i> Direct Test	Gen-Probe, San Diego, CA (Hologic)	<ul style="list-style-type: none"> <li>• Nonamplified</li> <li>• Sensitivity of 91.7%, specificity of 99.3%, and overall agreement of 97.4% vs culture</li> <li>• Turnaround time of 60 min</li> </ul>
Lyra Direct Strep Assay	Quidel Corp., San Diego, CA	<ul style="list-style-type: none"> <li>• Amplified</li> <li>• Sensitivity of 96.5%, specificity of 98.0%</li> <li>• All negative test results should be confirmed by bacterial culture</li> <li>• Turnaround time of &lt;70 min</li> </ul>
<i>illumigene</i> Group A <i>Streptococcus</i> DNA Amplification Assay	Meridian Bioscience, Cincinnati, OH	<ul style="list-style-type: none"> <li>• Amplified</li> <li>• Sensitivity of 98.0%, specificity of 97.7%</li> <li>• Turnaround time of &lt;60 min</li> </ul>

A number of studies have reported test characteristics for various nucleic acid amplification tests for GAS. The test characteristics of some of the amplified nucleic acid molecular diagnostics for GAS, with sensitivities and specificities compared with standard culture, are summarized in Table 8.

**Table 8. Summary of Amplified Nucleic Acid Detection Tests for GAS**

Study	Assay	Population	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Slinger et al (2011)	Laboratory-developed internally controlled GAS PCR assay	306 archived throat swab samples	96.0 (90.1 to 98.4)	98.6 (95.8 to 99.5)	96.9 (91.4 to 99.0)	98.1 (95.2 to 99.2)
Anderson et al (2013)	<i>illumigene</i> GAS assay	796 pharyngeal swabs (12.8% GAS culture-positive)	100 (95 to 100) (99 after discrepant analysis)	94.2 (92 to 95) (99.6 after discrepant analysis)	63.8 (54 to 72)	100 (99 to 100)
Henson et al (2013)	<i>illumigene</i> GAS assay	437 pharyngeal swabs (21.1% GAS)	100	95.9	NR	NR

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Study	Assay	Population	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Upton et al (2016)	Illumigene GAS assay	culture-positive) 757 pharyngeal swabs from school-based setting (12.2% GAS culture-positive)	82 (87 after discrepant analysis)	93 (98 after discrepant analysis)	61 (88 after discrepant analysis)	97 (97 after discrepant analysis)
Cohen et al (2015)	Alere i Strep A assay	481 pharyngeal swabs (30.4% GAS culture-positive)	95.9 (92.7 to 99.1) (98.7 after discrepant analysis)	94.6 (92.2 to 97.0) (98.5 after discrepant analysis)	88.7 (83.8 to 93.6) (96.9 after discrepant analysis)	98.1 (96.7 to 99.6) (99.4 after discrepant analysis)
Faron et al (2015)	AmpliVue GAS assay	1192 pharyngeal swabs (14.5% GAS culture-positive)	98.3 (95 to 100)	93.2 (91 to 95)	71.2	99.7
Boyanton et al (2016)	Lyra Direct Strep assay	161 pharyngeal swabs from patients with negative RADTs	100	100	100	100

CI: confidence interval; GAS: group A *Streptococcus*; NPV: negative predictive value; NR: not reported; PCR: polymerase chain reaction; PPV: positive predictive value; RADT: rapid antigen detection test.

In most studies of the amplified PCR assays, the sensitivity and specificity of the probes are very high. Upton et al (2016) reported lower sensitivity and lowered PPV for the Illumigene assay than previous studies using this assay. The authors hypothesized that the lower PPV might have been related to the fact that the study was conducted in a population of children attending school, lowering the pretest probability of actual GAS infection. Alternatively, the PCR assay might be detecting isolates of other *Streptococcus* species that carry the GAS pyrogenic exotoxin B gene, which is detected by the assay.

The high NPV of nucleic acid-based assays for GAS suggests that, as point-of-care tests, they offer improved accuracy over the current standard, rapid antigen detection tests. The high sensitivity, approaching that of standard culture, suggests that it may be reasonable to use them as an alternative to culture.

### **Streptococcus, Group B**

Several rapid PCR-based tests for GBS have been developed, with reported sensitivities and specificities similar to those of conventional culture. DNA probes have also been developed to identify GBS from cultured specimens. The use of intrapartum antibiotic therapy for GBS is recommended in patients who are known to be carriers for GBS. The postpartum management of newborn infants to prevent early-onset GBS infection is affected by whether the maternal GBS status is positive, negative, or unknown, and whether antibiotic prophylaxis is administered. The availability of rapid testing in peripartum women allows initiation or discontinuation of peripartum antibiotic prophylaxis to prevent vertical transmission of GBS.

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### ***Trichomonas vaginalis***

Nye et al (2009) compared the performance characteristics of PCR testing for *Trichomonas* with wet prep microscopy and culture in 296 female and 298 male subjects. In both women and men, DNA probe testing of vaginal swabs was more sensitive than culture. However, in men, wet prep testing was more sensitive than DNA probe testing. Munson et al (2010) compared DNA probe testing with culture in 255 vaginal saline preparations. The DNA probe identified *Trichomonas* in 9.4% (24/255) of specimens that were negative on culture. This probe offers the ability to better distinguish between causes of vaginitis, which can be difficult to assess clinically and the obviate the use of standard culture methods. Nucleic acid amplification tests have demonstrated higher clinical sensitivity than culture and wet mount microscopy, as well as single-probe nonamplified testing in general. A 2011 prospective multicenter study of 1025 asymptomatic and symptomatic women found nucleic acid amplification testing had a clinical sensitivity of 100% for both vaginal and endocervical swabs while urine specimen sensitivity was 95.2%. Specificity rates ranged from 98.9% to 99.6%. Other studies have also reported similar results. PCR amplification tests have higher clinical sensitivity and are considered the standard of care for diagnosing *Trichomonas vaginalis* when culturing is not an option.

### **SUMMARY OF EVIDENCE**

For individuals who have suspected *C. pneumoniae* who receive a nucleic acid probe for *C. pneumoniae*, the evidence includes prospective and retrospective evaluations of the tests' sensitivity and specificity. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, and change in disease status. The body of evidence is limited. One study was identified that reported relatively high sensitivity and specificity for a polymerase chain reaction–based test. However, the total number of patients in this study was small (N=56), and most other studies were conducted in the investigational setting. In addition to the limitations in the evidence base on test characteristics, the clinical implications of these tests are unclear. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have hepatitis who receive a nucleic acid probe for hepatitis G, the evidence is lacking. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, and change in disease status. The clinical implications of this test are unclear. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have signs and/or symptoms of gastroenteritis who receive nucleic acid–based gastrointestinal pathogen panel, the evidence includes prospective and retrospective evaluations of the tests' sensitivity and specificity. 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. However, in most instances, when a specific pathogen is suspected, individual tests could be ordered. There may be a subset of patients with an unusual presentation who would warrant testing for a panel of pathogens at once, but

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that subset has not been well defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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 02/04/2016 Medical Policy Committee review  
 02/17/2016 Medical Policy Implementation Committee approval. Reorganized policy statements and added new pathogens to coverage statements (enterovirus, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *hominus* and *genitalium* and *Bartonella*, *Megasphaera*, BVAB2 and *Atopobium vaginae*. and for quantified testing for human herpesvirus 6).. *Borrelia* testing removed from policy.  
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update  
 02/02/2017 Medical Policy Committee review  
 02/15/2017 Medical Policy Implementation Committee approval. No change to coverage.  
 02/01/2018 Medical Policy Committee review  
 02/21/2018 Medical Policy Implementation Committee approval. Coverage statement revised to track BCBSA.  
 10/08/2018 Coding update  
 Next Scheduled Review Date: 02/2019

### Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)<sup>®</sup>‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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*CPT is a registered trademark of the American Medical Association.*

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

Code Type	Code
CPT	0008U,87472,87475,87476, 87482,87483,87485,87486,87487,87492, 87498,87505,87506,87507,87512, 87525,87526,87527,87530, 87531, 87532, 87533, 87542, 87552, 87557, 87561,87562, 87582, 87592, 87652,87797,87798,87799,87800,87801 Deleted codes eff 1/1/18: 0004U, 87477, 87515
HCPCS	No codes

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# Louisiana

## Identification of Microorganisms Using Nucleic Acid Probes

Policy # 00488

Original Effective Date: 10/21/2015

Current Effective Date: 05/01/2018

ICD-10 Diagnosis	A15.6-A15.7	A30.0-A31.9	A48.1	A54.00-A54.09	A54.1
	A54.21-A54.29	A54.30-A54.39	A54.40-A54.49	A54.81-A54.89	A54.9
	A59.00-A59.09	A60.00-A60.09	A60.1	A60.9	A74.81
	A74.89	A74.9	B00.0-B00.4	B00.50-B00.59	B00.7
	B00.81-B00.89	B00.9	B16.0-B16.9	B17.10-B17.11	B18.0-B18.2
	B19.10-B19.11	B20	B25.0-B25.9	B33.8	B34.1-B34.8
	B96.82-B96.89	B97.19	B97.29	B97.5-B97.6	B97.81-B97.89
	J09.X1-J09.X9	J10.00-J10.08	J10.1-J10.2	J10.81-J10.89	J11.00
	J11.08	J11.1-J11.2	J11.81-J11.89	J12.9	J20.4
	P35.1-P35.9	P37.0-P37.9	Z21		
	Add codes eff 10/1/17:	Z36.0-Z36.9			

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

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

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

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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