Identification of Microorganisms Using Nucleic Acid Probes

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:

- Atopobium vaginae
- Bacterial Vaginosis Associated Bacteria 2 (BVAB2)
- 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
- Megasphaera species (Type 1 and Type 2)
- Mycobacterium species
- Mycobacterium tuberculosis
- Mycobacterium avium intracellulare
- Mycoplasma genitalium
- Mycoplasma hominis
- Mycoplasma pneumoniae
- Neisseria gonorrhoeae
- Respiratory virus panel
- Staphylococcus aureus
- Staphylococcus aureus, methicillin resistant
- Streptococcus, group A
- Streptococcus, group B
- Trichomonas vaginalis
- Ureasplasma urealyticum
- Treponema pallidum
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Policy # 00488
Original Effective Date: 10/21/2015
Current Effective Date: 02/15/2017

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

- Cytomegalovirus
- Hepatitis B virus
- Hepatitis C virus
- HIV-1
- HIV-2
- Human herpesvirus 6
- 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
- Gastrointestinal pathogen panel
- 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, C. albicans, may be considered medically necessary. For complicated infections, testing for multiple candida subspecies may be considered medically necessary. The Centers for Disease Control and Prevention classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or likely to be C. albicans; or in 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 (Centers for Disease Control and Prevention, 2010).
- In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared to traditional culture techniques is the rapidity of results. This advantage suggests that the most appropriate use of the DNA probe technique is in the setting of impending labor, for which prompt results could permit the initiation of intrapartum antibiotic therapy.
Many probes have been combined into panels of tests. For the purposes of this policy, other than the gastrointestinal pathogen panel and the respiratory virus panel, only individual probes are reviewed.

The use of molecular diagnostics for the diagnosis and management of Borrelia burgdorferi infection (Lyme disease) is addressed in policy 00173.

### CPT Codes for Nucleic Acid Probes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
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<td>Bacterial Vaginosis Associated Bacteria 2 (BVAB2)</td>
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<td><em>Enteroxivirus</em></td>
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<td><em>HIV-1</em></td>
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<td><em>HIV-2</em></td>
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<td>Human papillomavirus</td>
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<td>Influenza virus</td>
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<td><em>Megasphaera species</em> (Type 1 and 2)*</td>
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<td><em>Mycobacterium tuberculosis</em></td>
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<td><em>Mycoplasma genitalium</em></td>
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<td><em>Mycoplasma hominis</em></td>
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<td><em>Mycoplasma pneumoniae</em></td>
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<td>Respiratory virus panel</td>
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<td><em>Staphylococcus aureus</em>, methicillin-resistant</td>
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<td>87652</td>
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<tr>
<td><em>Streptococcus</em>, group B</td>
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<td><em>Treponema pallidum</em></td>
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<tr>
<td><em>Trichomonas vaginalis</em></td>
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</table>
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<thead>
<tr>
<th>Pathogen</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureasplasma urealyticum</td>
<td></td>
<td>87798</td>
<td></td>
</tr>
</tbody>
</table>

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

Nucleic acid probes are available for the identification of a wide variety of microorganisms, offering more rapid identification than standard cultures. Nucleic acid probes can also be used to quantitate the number of microorganisms present. This technology offers advantages over standard techniques when rapid identification is clinically important, when microbial identification using standard culture is difficult or impossible, and/or when treatment decisions are based on quantitative results.

In the past, identification of microorganisms was dependent either on 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.

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 PCR or reverse transcriptase (RT)-PCR. In addition to PCR, other nucleic acid amplification techniques have been developed such as transcription-mediated amplification, loop-mediated isothermal DNA amplification (LAMP), 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 give an assessment of how many microorganisms are present. Quantification of the amount 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.

In 1998, the CPT codes were revised to include a series of new codes that describe the direct probe technique, amplified probe technique, and quantification for 22 different microorganisms. These series of CPT codes were introduced as a group. In addition, CPT codes have been added for additional microorganisms, such as Staphylococcus aureus.

Comparison of Probe Techniques

The direct probe technique, amplified probe technique, and probe with quantification methods vary in terms of 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.
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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 (NASBA), transcription-mediated amplification (TMA), and strand displacement amplification (SDA). NASBA and TMA involve amplification of an RNA (rather than a DNA) target.

- **Probe amplification methods** include ligase chain reaction (LCR).

- **Signal amplification methods** include branched DNA probes (bDNA) and hybrid capture methods using an anti-DNA/RNA hybrid antibody.

The “probe with quantification” techniques refer 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 1.

**Table 1: Example Probe Methods**

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

Direct assays will generally have lower sensitivity than amplified probes. In practice, most commercially available probes are amplified, with a few exceptions. For the purposes of 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.

**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 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 (IFA) and one using enzyme immunosorbent assay (EIA), 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 diseased skin, throughout the entire gastrointestinal tract, expectorated sputum, the female genitalia, and in 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.

**Chlamydophila pneumoniae**

*Chlamydia pneumoniae* is an important cause of pneumonia, bronchitis, and sinusitis. Culture and isolation of the microorganism is difficult; a microimmunofluorescence serum test may be used. The use of PCR 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.
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Cytomegalovirus
Cytomegalovirus (CMV) is a common virus that infects many, 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 the HIV virus. CMV can also remain latent in tissues after recovery of the host from an acute infection. Diagnosis depends on 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 for 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 from 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 nonpolio enteroviruses that can cause disease in humans. Most people who are infected with a nonpolio enterovirus have no disease symptoms at all. Infected persons who develop illness usually develop either mild upper respiratory symptoms, flu-like symptoms with fever and muscle aches, or an illness with rash. Less commonly, some persons have "aseptic" or viral meningitis. 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 as a technique for monitoring the response to 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 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 PCR 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 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. Anti-viral treatment can be effective if instituted early in the course of 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. In addition, amplification techniques for Mycobacterium tuberculosis may be used in patients who have a positive smear. The rapid
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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, younger than 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 pneumonia* recover completely, although the course is sometimes prolonged for up to 4 weeks or more. Extrapulmonary complications of *M pneumonia* 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. Direct DNA probes and amplification techniques have also been used. Neisseria is often tested for at the same time as chlamydia.

**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 also been interest in evaluating the use of viral load tests of HPV 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. Throat culture is the preferred method for diagnosing *Streptococcus pharyngitis*. In addition, 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 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*, Streptococcus, group B (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, the American College of Obstetrics and Gynecology, and the American Academy of Pediatricians recommend 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 institution of antibiotics during labor.
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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. 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 at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/Ucm330711.htm
The Association of Molecular Pathology (AMP) website also provides a list of current FDA approved tests for diagnosis of infectious diseases (available online at: http://www.amp.org/FDATable/FDATable.pdf). Table 2 lists tests that are FDA-approved/cleared but do not have specific CPT codes.

Table 2. FDA-Approved/Cleared Tests Without CPT Codes

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

FISH: fluorescence in situ hybridization; 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
The clinical utility of the nucleic acid probes has been determined on the basis of direct published evidence and/or a chain of indirect evidence. Ideally, the determination that a specific nucleic acid probe has evidence to support its use would be based on the following:
- Is there evidence of analytic validity (test technical performance)?
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- Is there evidence of clinical validity (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV])?
- Is there either direct evidence or a chain of indirect evidence that there is clinical utility? Potential reasons for a nucleic acid probe to be associated with improved clinical outcomes compared with standard detection techniques include the following (note: in all cases, for there to be clinical utility, making a diagnosis should be associated with changes in clinical management, which could include initiation of effective treatment, discontinuation of other therapies, or avoidance of invasive testing):
  - Significantly improved speed and/or efficiency in making a diagnosis.
  - Improved likelihood of obtaining any diagnosis in cases where standard culture is difficult. Potential reasons for difficulty in obtaining standard culture include low numbers of the organisms (eg, HIV), fastidious or lengthy culture requirements (eg, Mycobacteria, Chlamydia, Neisseria species), or difficulty in collecting an appropriate sample (eg, herpes simplex encephalitis).
  - There is no way to definitively make a diagnosis without nucleic acid testing.
  - The use of nucleic acid probe testing provides qualitatively different information than that available from standard culture, 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.

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. These 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 of clinical interpretation of results. Amplification of organisms representing latent infection or colonization cannot be distinguished from active, clinically significant infections. In addition, amplification techniques may amplify fragments of nucleic acids, representing dead microorganisms, thus further clouding the clinical interpretation.

**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.

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 CFU/mL bacteria and greater than 50 CFU/mL bacteria, respectively. An earlier study 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 reported high sensitivity of a PCR-based enzyme immunoassay in human lymph node samples.
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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 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 (FFPE) cases of lymphadenitis with histologic and/or clinical suspicion of *B. henselae*. Control cases included 14 cases of lymphadenopathy. FFPE tissue sections were evaluated with a mAb to *B. henselae*, Steiner silver stain (SSS), and PCR that targeted *B. henselae* and *B. quintana*. Positive cases were as follows: SSS, 11 (46%); PCR, 9 (38%); and IHC, 6 (25%). Only 2 cases (8%) 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. SSS 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 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 in 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 real-time qPCR assay, developed for the detection of the most common 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 suggest that this assay may 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.
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**Chlamydia pneumonia or Chlamydia Trachomatis**

Probes are commercially available for the detection of *Chlamydia pneumonia* or *trachomatis*. A study by Stanek et al demonstrated a *Chlamydia*-specific real-time PCR which 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 *Chlamydia trachomatis* or *C pneumoniae*. Of 65 positive samples, 61 (93.8%) were found to be positive with the new PCR. Another study demonstrated the VERSANT® CT/GC DNA 1.0 Assay performed with 99.2% specificity for *Chlamydia trachomatis* detection and sensitivity of 100%.

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 compared tissue culture, PCR/EIA, direct fluorescent antibody (DFA) 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 gold standard, given the difficulty in culturing *C. pneumoniae*. However, when culture- and/or DFA-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.

**Clostridium difficile**

DNA probes for Clostridium difficile using PCR have been commercially available since 2009. Eastwood et al 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.

**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, 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 nonpolio enteroviruses that can cause disease in humans. Several FDA-approved test kits are available including the GeneXpert Enterovirus Assay (GXEA), with a 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 cerebrospinal fluid. GXEA showed a high specificity but a lower sensitivity for the detection of enterovirus RNA compared with the RT-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 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 are able to detect vancomycin resistance in a rapid and accurate manner 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, that were analyzed for bacterial vaginosis by both Gram stain using Nugent criteria and a DNA hybridization test (Affirm VPIII hybridization test).
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test). Of the 321 patients, 115 (35.8%) were Gram-positive for bacterial vaginosis and 126 (39.2%) were negative. A total of 80 patients (25.0%) 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 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 uses 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 demonstrate overall high sensitivities and specificities and indicate the panels may be useful for detecting causative agents for gastrointestinal infections. Studies suggest that panels limited to bacterial pathogens have similarly high sensitivities and specificities compared with bacterial culture. Beckmann et al 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 in 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. In addition, 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 include quantitative hepatitis B DNA levels in the diagnostic criteria for chronic and resolved hepatitis B and inactive hepatitis B carrier states.
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**Hepatitis C**

Diagnostic tests for hepatitis C can be divided into 2 general categories: (1) serological assays that detect antibody to hepatitis C virus (anti-HCV); and (2) molecular assays that detect, quantify, and/or characterize 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 if 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 real-time 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 utilized 4 reference strains and 42 HSV isolates obtained from patients between September 1998 and September 2004. These 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 pol 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.

**Herpes Virus-6**

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 of rt-PCR detecting viral mRNA transcripts in hematopoietic stem cell transplant (HSCT) 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, primary HHV-6 infection can cause severe disease
including thrombocytopenia, hepatitis, myocarditis, and meningoencephalitis. In immunosuppressed patients, particularly HSCT 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 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 HIV-1 quantification. Quantification is regularly done 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 HIV-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 also been research interest in exploring the relationship of 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 or not 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 HPV, and then, if positive, followed by colposcopy. It is hypothesized that colposcopy might be deferred if a low viral load were 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 indicate improved sensitivity of PCR for identifying influenza and distinguishing influenza from related viruses. Lassauieri et al used a multiplex RT-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 initiating antiviral therapy early in the course of illness (if indicated), there is clinical utility for the use of these tests.
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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 recent study compared the usefulness of 2 quantitative RT-PCR assays (qrt-PCRmip targeting L pneumophila, and qrt-PCR16S targeting all Legionella species) performed on lower respiratory tract (LRT) samples for diagnostic and prognostic purposes in 311 patients hospitalized for community-acquired pneumonia (CAP). The Now Legionella urinary antigen test from Binax (Portland, ME) was used as a reference test. One subset of 255 CAP patients admitted to Chambery hospital in 2005 and 2006 was evaluated and the sensitivities, specificities, PPVs and NPVs for both qrt-PCR tests were 63.6%, 98.7%, 77.7%, and 97.4%, respectively. Diederen et al evaluated the use of an rt-PCR assay for Legionella species in 151 subjects with respiratory infections, (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 reported a significantly higher sensitivity for PCR versus 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.

Mycobacterium Species

DNA probes are available to distinguish between Mycobacterium species. In a recent study, the extracted DNA specimens from Mycobacterium species and non-mycobacterial species were tested using peptide nucleic acid (PNA) 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 the detection of Mycobacteria by direct smear examination, mycobacterial culture, and PNA 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, PNA 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% (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 Mycobacterium tuberculosis infection. In a recent 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. This 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 are necessary for successful treatment of infection.

*Mycobacterium avium* and *Mycobacterium intracellulare*

DNA probes are available to diagnose *Mycobacterium avium* and *Mycobacterium intracellulare* infection. A recent study evaluated the performance of the GenoType Mycobacteria Direct (GTMD) 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 sputum, 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, and 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 GTMD test, 3 samples were identified to be *M intracellulare* and 1 sample 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. The GTMD test is a reliable, practical, and easy tool for rapid diagnosis of smear-negative pulmonary and extrapulmonary tuberculosis so that effective precautions may be taken and appropriate treatment may be initiated.

*Mycoplasma pneumonia*

Probes for *Mycoplasma pneumonia* have been developed. In 1 study using probes, a very high sensitivity and specificity for *M. pneumoniae* infection was reported (99.1% and 100%, respectively). Chalker et al 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 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 syndrome and refractory/severe pneumonia. At least 1 study suggests that inappropriate antibiotic use may worsen fulminant mycoplasma infection, and patients benefit from early administration of appropriate antimycoplasmal drugs with steroids.
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Neisseria gonorrhoeae
Probes for Neisseria gonorrhoeae have been developed for commercial use. These probes are often a combination test with C trachomatis. A recent study demonstrated 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 study demonstrated the VERSANT® CT/GC DNA 1.0 assay performed with 99.4% and 99.2% of specificity for N gonorrhoeae and C trachomatis detection, respectively, whereas sensitivity was 100% both for 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, demonstrate 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 study by Brittain-Long on a randomized population of 406 patients with access to a rapid- multiplex-PCR assay used to detect 13 viruses had lower antibiotic prescription rates (4.5% vs 12.3%, respectively) versus delayed identification with no significant difference in outcome at follow-up (p=0.359). Access to a rapid method for etiologic diagnosis of respiratory tract infections may 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 are able to not only distinguish between coagulase-negative Staphylococcus and S aureus, they can also detect methicillin-resistant species (MRSA) 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 substantial likelihood of MRSA, testing may be considered medically necessary 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 (RADTs) are widely used to diagnose GAS pharyngitis. RADTs are characterized by high specificity (approximately 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 3 (though not meant to be all-inclusive) offers some examples of tests, with data...
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provided on turnaround times, sensitivities and specificities, and other characteristics appearing on relevant package inserts.

Table 3: Examples of Commercially Available GAS Probes

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Gen-Probe Group A Streptococcus Direct Test | Gen-Probe Inc., San Diego, CA | • Nonamplified  
• Sensitivity of 91.7%, specificity of 99.3%, and overall agreement of 97.4% compared with culture  
• Turnaround time of 60 min |
| Lyra Direct Strep Assay | Quidel Corp., San Diego, CA | • Amplified  
• Sensitivity of 96.5%, specificity of 98.0%  
• All negative test results should be confirmed by bacterial culture  
• Turnaround time of <70 min |
| Illumigene Group A Streptococcus DNA Amplification Assay | Meridian Bioscience, Cincinnati, OH | • Amplified  
• Sensitivity of 98.0%, specificity of 97.7%  
• Turnaround time of <60 min |

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 4.

Table 4: Summary of Amplified Nucleic Acid Detection Tests for Group A Streptococcus

<table>
<thead>
<tr>
<th>Study</th>
<th>Assay</th>
<th>Population</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slinger et al (2011)</td>
<td>Laboratory-developed internally controlled GAS PCR assay</td>
<td>306 archived throat swab samples</td>
<td>96.0% (90.1% to 98.4%)</td>
<td>98.6% (95.8% to 99.5%)</td>
<td>96.9% (91.4% to 99.0%)</td>
<td>98.1% (95.2% to 99.2%)</td>
</tr>
<tr>
<td>Anderson et al (2013)</td>
<td>Illumigene GAS assay</td>
<td>796 pharyngeal swabs (12.8% GAS culture positive)</td>
<td>100% (95% to 100%) (99% after discrepant analysis)</td>
<td>94.2% (92% to 95%) (99.6% after discrepant analysis)</td>
<td>63.8% (54% to 72%)</td>
<td>100% (99% to 100%)</td>
</tr>
<tr>
<td>Henson et al (2013)</td>
<td>Illumigene GAS assay</td>
<td>437 pharyngeal swabs (21.1% GAS culture positive)</td>
<td>100%</td>
<td>95.9%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Upton et al (2015)</td>
<td>Illumigene GAS assay</td>
<td>757 pharyngeal swabs from school-based setting (12.2% GAS culture)</td>
<td>82% (87% after discrepant analysis)</td>
<td>93% (98% after discrepant analysis)</td>
<td>61% (88% after discrepant analysis)</td>
<td>97% (97% after discrepant analysis)</td>
</tr>
</tbody>
</table>
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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)

1192 pharyngeal swabs (14.5% GAS culture positive) 98.3% (95 to 100%) 93.2 (91% to 95%) 71.2% 99.7%

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 reported lower sensitivity and lower PPV for the Illumigene assay than previous studies using this assay. The authors hypothesize that the lower PPV may be 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 may 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, RADTs. 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 different rapid PCR-based tests for group B Streptococcus (GBS) have been developed, with reported sensitivities and specificities similar to that 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.

**Trichomonas vaginalis**
Nye et al 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
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of vaginal swabs was more sensitive than culture. However, in men, wet prep testing was more sensitive than DNA probe testing. Munson et al compared DNA probe testing and 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 clinically and using 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 clinical sensitivity of 100% for both vaginal and endocervical swabs while urine specimen sensitivity was 95.2%. Specificity levels 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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for the use of nucleic acid probes for *Chlamydophila pneumoniae* or hepatitis G virus in individuals with suspected *C. pneumoniae* or with hepatitis, respectively, 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 for both types of organisms. For *C. pneumoniae*, 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.

The evidence for the use of a nucleic acid-based gastrointestinal pathogen panel in individuals who have signs and/or symptoms of gastroenteritis 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 that subset has not been well defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

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76. Package Insert, GenProbe. Group A Streptococcus Direct Test.

Policy History
Original Effective Date: 10/21/2015
Current Effective Date: 02/15/2017
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. New Policy.

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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, hominis 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.
10/01/2017 Coding update

Next Scheduled Review Date: 02/2018

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New code eff 1/1/17: 87483

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