Medical Policy

Identification of Microorganisms Using Nucleic Acid Probe

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Policy Number: 555

BCBSA Reference Number: 2.04.10
NCD/LCD: Local Coverage Determination (LCD): Infectious Disease Molecular Diagnostic Testing (L33433)

Related Policies
- Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease, #171
- Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis, #711

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of nucleic acid testing using a direct or amplified probe technique (without quantification of viral load) may be considered MEDICALLY NECESSARY 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.

Policy Guidelines
- CPT code 87481 is only medically necessary for severe, treatment resistant Candida infection with amplified probe technique.
- The use of molecular diagnostics for the diagnosis and management of Borrelia burgdorferi infection (Lyme disease) is addressed in policy #171.
- 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 nucleic acid testing using a direct or amplified probe technique (with or without quantification of viral load) may be considered MEDICALLY NECESSARY for the following microorganisms:
- Cytomegalovirus
- Hepatitis B virus
- Hepatitis C virus
- HIV-1
- HIV-2
- Human herpesvirus 6
- Influenza virus.

The use of nucleic acid testing using a direct or amplified probe technique with or without quantification of viral load is considered INVESTIGATIONAL for the following microorganisms:
- Chlamydia pneumoniae
- Hepatitis G virus
- Gastrointestinal pathogen panel.

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.

The use of nucleic acid testing using amplified probe technique with or without quantification of viral load is considered MEDICALLY NECESSARY for the following microorganisms:
- Babesiosis
- Ehrlichiosis, unspecified
- Tick-borne rickettsiosis, unspecified.
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Infectious Disease Molecular Diagnostic Testing (L33433)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
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<tbody>
<tr>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>87470</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, direct probe technique</td>
</tr>
<tr>
<td>87471</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, amplified probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, amplified probe technique, includes reverse transcription when performed</td>
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<td>87536</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed</td>
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<td>87537</td>
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<td>Code</td>
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<tr>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
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<td>87541</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, amplified probe technique</td>
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<td>87550</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, direct probe technique</td>
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<td>87551</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, amplified probe technique</td>
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<tr>
<td>87555</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, direct probe technique</td>
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<td>87556</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, amplified probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, direct probe technique</td>
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<tr>
<td>87561</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, amplified probe technique</td>
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<td>87580</td>
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<tr>
<td>87581</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, amplified probe technique</td>
</tr>
<tr>
<td>87590</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, direct probe technique</td>
</tr>
<tr>
<td>87591</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique</td>
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<tr>
<td>87623</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)</td>
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<td>87624</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)</td>
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<td>87625</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets</td>
</tr>
<tr>
<td>87632</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets</td>
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<tr>
<td>87633</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets</td>
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<tr>
<td>87640</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, amplified probe technique</td>
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<tr>
<td>87641</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, methicillin resistant, amplified probe technique</td>
</tr>
<tr>
<td>87650</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, direct probe technique</td>
</tr>
</tbody>
</table>
The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>87651</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, amplified probe technique</td>
</tr>
<tr>
<td>87653</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group B, amplified probe technique</td>
</tr>
<tr>
<td>87660</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique</td>
</tr>
<tr>
<td>87661</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique</td>
</tr>
<tr>
<td>87472</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, quantification</td>
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<tr>
<td>87475</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, direct probe technique</td>
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<td>87476</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, amplified probe technique</td>
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<td>87477</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, quantification</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Candida species, quantification</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, direct probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, amplified probe technique</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, quantification</td>
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<td>87492</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets</td>
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<tr>
<td>87506</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets</td>
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<tr>
<td>87507</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets</td>
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<td>87512</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, amplified probe technique</td>
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<tr>
<td>87527</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, quantification</td>
</tr>
</tbody>
</table>
**Description**

**Standard Microorganism Detection Techniques**
Classically, identification of microorganisms relied 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.

**Nucleic Acid Probe Techniques**
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 (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.

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™ VPIII Microbial Identification System (Becton, Dickinson, Franklin Lakes, NJ)</td>
<td><em>Candida, Gardnerella, Trichomonas species</em></td>
</tr>
<tr>
<td></td>
<td>GasDirect (Hologic, Bedford, MA)</td>
<td><em>Group A 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® 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 immunoassay (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. The diagnosis of vaginitis is addressed separately in policy #711.

*Chlamydophila pneumoniae*
*Chlamydophila pneumoniae* is an important cause of pneumonia, bronchitis, and sinusitis. Culture and isolation of the microorganism is difficult; a micro-immunofluorescence 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.

*Cytomegalovirus*
Cytomegalovirus (CMV) is a common virus that infects many, but rarely causes clinical disease in healthy individuals. However, this virus can cause protein 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 non-polio enteroviruses that can cause disease in humans. Most people who are infected with a non-polio 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, 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. Diagnosis of bacterial vaginosis is addressed separately in policy #711.

**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 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.¹

**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. Antiviral 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 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. 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, 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.

**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 streptococcal 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*, 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, 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.

**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.

**Summary**

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.

The evidence for the use of nucleic acid probes for *Chlamydia 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.

For other nucleic acid probes discussed in this review, the tests' clinical utility was evaluated based on whether there is demonstrated clinical validity, along with either direct evidence of improved outcomes or a chain of logic 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 empiric antibiotics pending culture results. In many cases, clinical input indicated that nucleic acid-based testing is considered the standard of care (eg, hepatitis B and C, HIV-1 and -2, and cytomegalovirus in the post-transplant setting).

**Policy History**

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<td>8/2016</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


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


Endnotes

1 Based on expert opinion