Title: Identification of Microorganisms Using Nucleic Acid Testing

See Also:  
- Influenza Virus Diagnostic Testing and Treatment in the Outpatient Setting  
- Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Professional
Original Effective Date: July 8, 2008  
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Institutional
Original Effective Date: July 16, 2009  
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## DESCRIPTION

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

### Objective

The objective of this evidence review is to determine whether testing for microorganisms using nucleic acid probes improves the net health outcome in individuals with suspected infections.

### BACKGROUND

#### 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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
• With suspected Chlamydia pneumoniae infection | Interventions of interest are:  
• Nucleic acid probe for Chlamydia pneumoniae | Comparators of interest are:  
• No Chlamydia pneumoniae-specific testing | Relevant outcomes include:  
• Test accuracy  
• Test validity  
• Other test performance measures  
• Symptoms  
• Change in disease status |
| Individuals:  
• With hepatitis | Interventions of interest are:  
• Nucleic acid probe for hepatitis G | Comparators of interest are:  
• No hepatitis G–specific testing | Relevant outcomes include:  
• Test accuracy  
• Test validity  
• Other test performance measures  
• Symptoms  
• Change in disease status |
| Individuals:  
• With signs and/or symptoms of gastroenteritis | Interventions of interest are:  
• Nucleic acid–based gastrointestinal pathogen panel | Comparators of interest are:  
• No gastrointestinal pathogen-specific testing  
• Culture or nucleic acid–based testing for individual pathogens | Relevant outcomes include:  
• Test accuracy  
• Test validity  
• Other test performance measures  
• Symptoms  
• Change in disease status |
| Individuals:  
• With signs and/or symptoms of meningitis and/or encephalitis | Interventions of interest are:  
• Nucleic acid–based central nervous system pathogen panel | Comparators of interest are:  
• No central nervous system pathogen-specific testing  
• Culture or nucleic acid–based testing for individual pathogens | Relevant outcomes include:  
• Test accuracy  
• Test validity  
• Other test performance measures  
• Symptoms  
• Change in disease status |
**Bartonella henselae or quintana**

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

*Bartonella* may also cause an opportunistic infection in HIV-infected patients, in whom it is characterized by an acute febrile bacteremic illness, evolving to an asymptomatic bacteremia and finally indolent vascular skin lesions. The organism is typically detected using culture techniques, although an incubation period of 5 to more than 30 days is required. DNA probe technology has been investigated as a diagnostic technique. *Bartonella quintana* has classically been associated with “trench fever,” which is characterized by systemic symptoms (bone pain, malaise, headache), along with recurring fevers of varying durations. Among HIV-infected patients, *B. quintana* has been associated with bacillary angiomatosis.

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

**Candida Species**

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

**Chlamydia pneumoniae**

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

**Chlamydia trachomatis**

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

**Cytomegalovirus**

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

**Clostridium difficile**

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

**Enterovirus**

Enteroviruses are single-stranded RNA viruses. This group of viruses includes the polioviruses, coxsackieviruses, echoviruses, and other enteroviruses. In addition to 3 polioviruses, there are more than 60 types of non-polio enteroviruses that can cause disease in humans. Most people who are infected with a non-polio *enterovirus* have no disease symptoms. Infected persons who develop illness usually develop either mild upper respiratory symptoms, flu-like symptoms with fever and muscle aches, or an illness with rash. Less commonly, enteroviruses can cause “aseptic” or viral meningitis, encephalitis, acute paralysis, and/or myocarditis. Enteroviral infections can cause life-threatening systemic infections in neonates, which are often associated with myocarditis or fulminant hepatitis. The use of amplified probe DNA test(s) can be used to detect enteroviruses.
**Gardnerella vaginalis**
A common microorganism, *Gardnerella vaginalis* is typically found in the human vagina and is usually asymptomatic. However, *G. vaginalis* is found in virtually all women with bacterial vaginosis and is characterized by inflammation and perivaginal irritation. The microorganism is typically identified by culture. The role of *G. vaginalis* in premature rupture of membranes and preterm labor is also under investigation.

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

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

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

In immunosuppressed patients, HHV-6 reactivation may cause meningitis, encephalitis, pneumonitis, and/or bone marrow suppression.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 the disease. Therefore, rapid identification of influenza virus is important in making treatment decisions for high-risk patients and in instituting infection-control practices.

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

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

Mycoplasma pneumoniae
Mycoplasma pneumoniae is an atypical bacterium that is a common cause of pneumonia. It is most prevalent in younger patients below age 40 years and in individuals who live or work in crowded areas such as schools or medical facilities. The infection is generally responsive to antibiotics of the macrolide or quinolone class. Most patients with M. 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 been interest in evaluating the use of viral load tests of human papillomavirus to identify patients at highest risk of progressing to invasive cervical carcinoma.

**Streptococcus, Group A**

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

**Streptococcus, Group B**

Also referred to as *Streptococcus agalactiae*, group B streptococcus (GBS), is the most common cause of sepsis, meningitis, or death among newborns. Early-onset disease, within 7 days of birth, is related to exposure to GBS colonizing the mother’s anogenital tract during birth. The Centers for Disease Control and Prevention have recommended either maternal risk assessment or screening for GBS in the perinatal period.2 Screening consists of obtaining vaginal and anal specimens for culture at 35 to 37 weeks of gestation. The conventional culture and identification process requires 48 hours. Therefore there has been great interest in developing rapid assays using DNA probes to shorten the screening process so that screening could be performed in the intrapartum period with the institution of antibiotics during labor.

**Trichomonas vaginalis**

*Trichomonas* is a single-cell protozoan that is a common cause of vaginitis. The organism is sexually transmitted and can infect the urethra or vagina. The most common way of diagnosing *Trichomonas* is by clinical signs and by directly visualizing the organism by microscopy in a wet prep vaginal smear. The culture of *Trichomonas* is limited by poor sensitivity. Treatment with metronidazole results in a high rate of eradication. The disease is usually self-limited without sequelae, although infection has been associated with premature birth and higher rates of HIV transmission, cervical cancer, and prostate cancer.
Regulatory Status
A list of current U.S. Food and Drug Administration-approved or cleared nucleic acid-based microbial tests is available online.\(^3\) Table 1 lists tests approved or cleared by the Food and Drug Administration that do not have specific CPT codes.

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

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

Note: A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy.

A. The use of nucleic acid testing using a direct or amplified probe technique (without quantification of viral load) may be considered medically necessary (med nec) for the following microorganisms (see Policy Guidelines):

NOTE: (med nec) in the chart below applies only when the service is clinically indicated.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bartonella henselae</em> or <em>quintana</em></td>
<td>87797 (med nec)</td>
<td>87471 (med nec)</td>
<td>87472 (E/I)</td>
</tr>
<tr>
<td><em>Candida</em> species (See Policy Guidelines #3)</td>
<td>87480 (med nec)</td>
<td>87481 (med nec)</td>
<td>87482 (E/I)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>87490 (med nec)</td>
<td>87491 (med nec)</td>
<td>87492 (E/I)</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>87493 (med nec)</td>
<td>87798 (med nec)</td>
<td>87799 (E/I)</td>
</tr>
<tr>
<td><em>Enterococcus</em>, vancomycin resistant (eg, enterococcus vanA, vanB)</td>
<td>87797 (med nec)</td>
<td>87500 (med nec)</td>
<td>87799 (E/I)</td>
</tr>
<tr>
<td><em>Enterovirus</em></td>
<td>87797 (med nec)</td>
<td>87498 (med nec)</td>
<td>87799 (E/I)</td>
</tr>
<tr>
<td><em>Gardnerella vaginalis</em></td>
<td>87510 (med nec)</td>
<td>87511 (med nec)</td>
<td>87512 (E/I)</td>
</tr>
<tr>
<td>Gastrointestinal Pathogen Panel</td>
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<tr>
<td><em>Legionella pneumophila</em></td>
<td>87540 (med nec)</td>
<td>87541 (med nec)</td>
<td>87542 (E/I)</td>
</tr>
<tr>
<td>Meningitis / Encephalitis Panel</td>
<td>N/A</td>
<td>87483 (med nec)</td>
<td>N/A</td>
</tr>
<tr>
<td><em>Mycobacterium</em> species</td>
<td>87550 (med nec)</td>
<td>87551 (med nec)</td>
<td>87552 (E/I)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>87555 (med nec)</td>
<td>87556 (med nec)</td>
<td>87557 (E/I)</td>
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<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>87580 (med nec)</td>
<td>87581 (med nec)</td>
<td>87582 (E/I)</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>87590 (med nec)</td>
<td>87591 (med nec)</td>
<td>87592 (E/I)</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>87797 (med nec)</td>
<td>87634 (med nec)</td>
<td>N/A</td>
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<tr>
<td>Respiratory Virus Panel</td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>87797 (med nec)</td>
<td>87640 (med nec)</td>
<td>87799 (E/I)</td>
</tr>
</tbody>
</table>
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 "(med nec)" for the following microorganisms:

NOTE: (med nec) in the chart below applies only when the service is clinically indicated.

CPT codes 87797 and 87798 describe the use of direct probe and amplified probe respectively for infectious agents not otherwise specified. The following may be considered medically necessary (not an all-inclusive list):

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
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</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>87495 (med nec)</td>
<td>87496 (med nec)</td>
<td>87497 (med nec)</td>
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<tr>
<td>Hepatitis B virus</td>
<td>87797 (med nec)</td>
<td>87516 (med nec)</td>
<td>87517 (med nec)</td>
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<tr>
<td>Hepatitis C virus</td>
<td>87520 (med nec)</td>
<td>87521 (med nec)</td>
<td>87522 (med nec)</td>
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<tr>
<td>HIV-1</td>
<td>87534 (med nec)</td>
<td>87535 (med nec)</td>
<td>87536 (med nec)</td>
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<tr>
<td>HIV-2</td>
<td>87537 (med nec)</td>
<td>87538 (med nec)</td>
<td>87539 (med nec)</td>
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<tr>
<td>Human herpesvirus-6</td>
<td>87531 (med nec)</td>
<td>87532 (med nec)</td>
<td>87533 (med nec)</td>
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<tr>
<td>Influenza virus</td>
<td>See medical policy titled: Influenza Virus Diagnostic Testing and Treatment in the Outpatient Setting</td>
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<tr>
<td>Microorganism</td>
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<tr>
<td>12. <em>Leishmania</em></td>
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<td>13. <em>Yersinia pestis</em></td>
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<td>14. Actinomyces</td>
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<tr>
<td>15. Babesiosis (<em>Babesia</em>)</td>
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<td>16. Beta-tyrosinase</td>
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<td>17. BK polyomavirus</td>
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<tr>
<td>18. <em>Bordetella pertussis</em> and <em>B. parapertussis</em></td>
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<td>19. <em>Borrelia miyamotoi</em></td>
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<tr>
<td>20. <em>Brucella spp.</em></td>
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<tr>
<td>21. <em>Burkholderia</em> infections</td>
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<tr>
<td>22. Chancroid (<em>Haemophilus ducreyi</em>)</td>
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<tr>
<td>23. Chikungunya virus</td>
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<td>24. Colorado tick fever virus</td>
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<td>25. Ebola</td>
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<tr>
<td>26. Ehrlichiosis (<em>Ehrlichia</em>)</td>
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<tr>
<td>27. <em>Entamoeba histolytica</em></td>
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<tr>
<td>28. Epidemic typhus (<em>Rickettsia prowazekii</em>)</td>
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<tr>
<td>29. <em>Epstein Barr Virus</em> (EBV)</td>
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<tr>
<td>30. <em>Haemophilus influenza</em></td>
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<tr>
<td>31. Hantavirus</td>
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<tr>
<td>32. Hemorrhagic fevers of the family <em>Bunyaviridae</em> (Rift Valley fever, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndromes) - clinical presentation suggestive of these conditions</td>
<td></td>
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<tr>
<td>33. Hepatitis D virus</td>
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<tr>
<td>34. Hepatitis E virus</td>
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<tr>
<td>35. Human granulocytic anaplasmosis (<em>Anaplasmaphagocytophilum</em> [formerly <em>Ehrlichia phagocytophilum</em>])</td>
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<tr>
<td>36. Human T Lymphotropic Virus type 1 and type 2 (HTLV-I and HTLV-II)</td>
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<td>37. JC polyomavirus</td>
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<td>38. Malaria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. Measles virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. Microsporidia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. Mumps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42. <em>Mycoplasma hominis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43. <em>Neisseria meningitides</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. Parvovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45. Psittacosis (<em>Chlamydophila (Chlamydia) psittaci</em>)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46. Rocky Mountain Spotted Fever (<em>Rickettsia rickettsii</em>)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47. Rubella</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48. Severe acute respiratory syndrome (SARS) (coronavirus)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49. Shiga toxin (from <em>E. coli</em> and Shigella)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50. Syphilis (<em>Treponema pallidum</em>)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Microorganism

<table>
<thead>
<tr>
<th>Microorganism</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>51. Toxoplasma gondii</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52. Ureaplasma urealyticum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53. Varicella-Zoster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54. West Nile Virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55. Whipple's disease (T. whippeli)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D. CPT code 87799 describes the use of quantification for infectious agents not otherwise specified. The following may be considered **medically necessary**:
1. *Adenovirus* viral load
2. BK polyomavirus viral load
3. Epstein Barr viral load

E. The Respiratory Virus Panel (CPT codes 87631, 87632, 87633, 0098U, 0099U, 0100U, 0115U) will be **reviewed for medical necessity** on a case-by-case basis.

F. The Gastrointestinal Pathogen Panel (CPT codes 87505, 87506, 87507, 0097U) may be considered **medically necessary** in patients with:
1. Severe diarrhea longer than 72 hours in duration, **OR**
2. Severe diarrhea and ONE of the following:
   a) bloody stools, **OR**
   b) fever, **OR**
   c) the patient is immunocompromised.

G. The use of nucleic acid testing using a direct or amplified probe technique (*with or without* quantification of viral load) is considered **experimental / investigational** for the following microorganisms:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See medical policy titled: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>87485 (E/I)</td>
<td>87486 (E/I)</td>
<td>87487 (E/I)</td>
</tr>
<tr>
<td>Hepatitis G virus</td>
<td>87525 (E/I)</td>
<td>87526 (E/I)</td>
<td>87527 (E/I)</td>
</tr>
</tbody>
</table>

H. The use of nucleic acid testing for indications not addressed in the above policy are considered **experimental / investigational**.

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.

Note: If NOC codes 87797, 87798, 87799 are billed for PCR for microorganisms when specific codes exist, the claim will be returned for correct coding.

**Policy Guidelines**

1. 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.

2. 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.

3. 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 (2015) classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or in nonimmunocompromised women as likely to be caused by *C. albicans*. Complicated vulvovaginal candidiasis is classified as being recurrent or severe; or in women with uncontrolled diabetes, debilitation, or immunosuppression as less likely to be caused by a *C. albicans* species.

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

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

**RATIONALE**

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through October 18, 2018.

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

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose.
For some nucleic acid probes discussed in this review, the tests’ clinical utility was evaluated based on whether there is demonstrated clinical validity, along with either direct evidence of improved outcomes or a chain of evidence indicating that changes in management leading to improved outcomes are likely to occur with testing. For example, for group A *Streptococcus*, use of nucleic acid-based testing can result in a reduction in antibiotic use as a result of not needing to initiate empirical antibiotics pending culture results.

**Nucleic acid probes**

**Clinical Context and Test Purpose**

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

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

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

**Patients**

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

**Interventions**

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

The direct probe technique, amplified probe technique, and probe with quantification methods vary regarding the degree to which the nucleic acid is amplified and the method for measurement of the signal.

The direct probe technique refers to detection methods in which nucleic acids are detected without an initial amplification step.

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

- Target amplification methods include PCR (including PCR using specific probes, nested or multiplex PCR), nucleic acid-based sequence amplification, transcription-mediated amplification, and strand displacement amplification. Nucleic acid-based sequence
amplification and transcription-mediated amplification involve amplification of an RNA (rather than a DNA) target.

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

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

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

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

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

- Potential reasons for a nucleic acid probe to be associated with improved clinical outcomes compared with standard detection techniques include the following (note: in all cases, for there to be clinical utility, making a diagnosis should be associated with changes in clinical management, which could include initiation of effective treatment, discontinuation of other therapies, or avoidance of invasive testing):
  - Significantly improved speed and/or efficiency in making a diagnosis.
  - Improved likelihood of obtaining any diagnosis in cases where standard culture is difficult. Potential reasons for difficulty in obtaining standard culture include low numbers of the organisms (eg, HIV), fastidious or lengthy culture requirements (eg, Mycobacteria, Chlamydia, Neisseria species), or difficulty in collecting an appropriate sample (eg, herpes simplex encephalitis).
  - There is no way to definitively make a diagnosis without nucleic acid testing.
  - The use of nucleic acid probe testing provides qualitatively different information than that available from standard cultures, such as information regarding disease prognosis or response to treatment. These include cases where quantification of viral load provides prognostic information or is used to measure response to therapy.

**Timing**
Nucleic acid probes offer rapid detection; therefore, the timing of outcomes of interest is days following testing.
Setting
Patients may present with signs and symptoms of potential infections in primary care or emergency care.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity and Clinical Utility

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 colony-forming unit per milliliter of bacteria and greater than 50 colony-forming unit per milliliter of bacteria, respectively. An earlier study (2000) demonstrated high sensitivity of a PCR-based assay for the Bartonella riboflavin synthase gene in bacterial samples and samples from feline samples and human lymph node samples. Another study (1999) reported high sensitivity of a PCR-based enzyme immunoassay in human lymph node samples.

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

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

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

**Candida Species**

*Candida* infections are most commonly caused by *Candida albicans*, but other species may be responsible. In complicated or severe cases (eg, candidemia and invasive focal infections) or compromised patients, it may be necessary to identify the infecting *Candida* species for appropriate treatment planning. DNA probes are available to aid in the diagnosis of possible *Candida* species infections. Amplified peptide nucleic acid tests have demonstrated high sensitivity and specificity levels of up to 100%. Some tests have been able to detect up to 6 *Candida* species. A rt-PCR assay, developed for the detection of the most common pathogenic *Candida* species using a single-reaction PCR assay targets a selected region of the 28S subunit of the fungal rDNA gene. In a 2012 study, the sensitivity and specificity of an assay based on quantitative real-time assay using duplex mutation primers were 100% and 97.4%, respectively. The data suggested that this assay might be appropriate for use in clinical laboratories as a simple, low-cost, and rapid screening test for the most frequently encountered *Candida* species.

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

**Chlamyphilia pneumoniae or Chlamydia trachomatis**

**Clinical Context and Test Purpose**

The purpose of nucleic acid probe for *Chlamyphilia pneumoniae* is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with suspected *Chlamyphilia pneumoniae* infection.

The question addressed in this evidence review is: does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with suspected *Chlamyphilia pneumoniae* infection?

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

**Patients**

The relevant population of interest are individuals with suspected *Chlamyphilia pneumoniae* infection.

**Interventions**

The intervention being considered is testing using a nucleic acid probe for *Chlamyphilia pneumoniae*.
Comparators
Comparators of interest include no *Chlamyphila pneumoniae*-specific testing and culture or direct fluorescent antibody stain.

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, symptoms, and change in disease status.

Timing
Though not completely standardized, follow-up for suspected *Chlamyphila pneumoniae* infection symptoms would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.

Setting
Patients with suspected *Chlamyphila pneumoniae* infection are actively managed by primary care providers in outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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

For *C. trachomatis*, microbial culture is technically difficult, and nucleic acid amplification tests for *C. trachomatis* are generally preferred over other diagnostic methods, including direct fluorescent antibody tests, enzyme immunoassays, and nucleic acid hybridization tests. Diagnosis of *C. trachomatis* has clinical utility in a variety of settings. Treatment of individuals with *C. trachomatis* genital infection prevents sexual transmission and complications, including pelvic inflammatory disease. Treatment of pregnant women will prevent the transmission of infection to infants during delivery. Antibiotic treatment is indicated in neonatal conjunctivitis caused by *C. trachomatis*.
PCR-based tests specific for *C. pneumoniae* have been described in the investigational setting.\(^{16,17}\) Gaydos et al (1994) compared with tissue culture, PCR enzyme immunosorbent assay, direct fluorescent antibody stain, and serology for the diagnosis of *C. pneumoniae* in 56 patients with respiratory symptoms and 80 asymptomatic individuals.\(^{17}\) Determining test characteristics is limited by the lack of a true criterion standard, given the difficulty in culturing *C. pneumoniae*. However, when culture- and/or direct fluorescent antibody-positive results were used as a reference, PCR had a sensitivity and specificity of 76.5% and 99.0%, respectively. However, the use of PCR-based tests for *C. pneumoniae* in clinical practice has not been well defined.

**Section Summary: Chlamyphila pneumoniae or Chlamydia trachomatis**

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

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

**Clostridium difficile**

DNA probes for *Clostridium difficile* using PCR have been commercially available since 2009.\(^{18,19,20,21}\) Eastwood et al (2009) compared the performance characteristics of numerous DNA probes with cytotoxic assays and cultures.\(^{19}\) The results demonstrated a mean sensitivity of 82.8% (range, 66.7%-91.7%) and a mean specificity of 95.4% (range, 90.9%-98.8%).

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

**Central Nervous System Bacterial and Viral Panel**

**Clinical Context and Test Purpose**

The purpose of nucleic acid-based central nervous system pathogen panel is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with signs and/or symptoms of meningitis and/or encephalitis.

The question addressed in this evidence review is: does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with suspected meningitis and/or encephalitis?

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

**Patients**

The relevant population of interest are individuals with signs and/or symptoms of meningitis and/or encephalitis.

**Interventions**

The therapy being considered is nucleic acid-based central nervous system pathogen panel.
Comparators
Comparators of interest include no central nervous system pathogen-specific testing and culture or nucleic acid-based testing for individual pathogens.

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, symptoms, and change in disease status.

Timing
Though not completely standardized, follow-up for suspected meningitis and/or encephalitis would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.

Setting
Patients with signs and/or symptoms of meningitis and/or encephalitis are actively managed by infectious disease specialists and emergency medicine professionals in an emergency or inpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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

The FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics, Salt Lake City, UT) is a nucleic acid-based test that simultaneously detects multiple bacterial, viral, and yeast nucleic acids from CSF specimens obtained via lumbar puncture from patients with signs and/or symptoms of meningitis and/or encephalitis. The test has been cleared for marketing through the U.S. Food and Drug Administration 510(k) process. The test identifies 14 common organisms responsible for community-acquired meningitis or encephalitis:
- Bacteria: *Escherichia coli* K1; *Haemophilus influenzae*; *Listeria monocytogenes*; *Neisseria meningitides*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*
- Viruses: Cytomegalovirus; *Enterovirus*; *Herpes simplex virus 1*; *Herpes simplex virus 2*; Human herpesvirus 6; *Human parechovirus*; *Varicella zoster virus*
- Yeast: *Cryptococcus neoformans/gattii*

Run-time is approximately 1 hour per specimen.
The clinical validity of the test has been analyzed using 1560 CSF specimens collected at 11 U.S. sites and several smaller studies. The following study selection criteria were used to assess whether the central nervous system panel is clinically valid: (1) eligibility and selection are described, and the study population represents the population of interest; (2) the test is compared with a credible reference standard; (3) studies report sensitivity, specificity, and preferably predictive values; studies that completely report true- and false-positive results are ideal. Several studies failed to meet selection criteria.22,23,24,25,26,27 The study characteristics and results of selected studies are shown in Tables 3 and 4.

In the largest study by Leber et al (2016), 1560 samples were tested,28. The samples were from children and adults with available CSF but not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis. Even the most prevalent organisms were present only a small number of times in the samples. The specificities ranged from 98% to 100% and, given the high number of true negatives, the specificities were estimated with tight precision. However, given the small number of true positives, the sensitivities to detect any given organism could not be estimated with precision. A total of 141 pathogens were detected in 136 samples with the FilmArray and 104 pathogens detected using comparator methods; 43 FilmArray results were “false-positive” compared with the comparator method and six were “false-negative.” For 21 of the 43 “false-positives,” repeat testing of the FilmArray, comparator, or additional molecular testing supported the FilmArray results. The remaining 22 “false-positives” (16% of all positives) were unresolved. Codetections were observed in 3.7% (5/136) positive specimens. All five included a bacterial and viral positive result, and all 5 specimens were found to have a false-positive result demonstrated by comparator testing. The investigators suggested that the discrepancies could have been due to specimen contamination or another problem with the assay configuration or testing process.

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

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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Timing of Reference and Index Tests</th>
<th>Blinding of Assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber et al (2016)</td>
<td>Children and adults from whom a CSF specimen was available from standard care testing for bacterial culture; not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis</td>
<td>Nonconcurrent prospective</td>
<td>Culture and PCR</td>
<td>Processed within 7 d of collection or immediately frozen for future testing</td>
<td>Yes</td>
</tr>
<tr>
<td>Hanson et al (2016)</td>
<td>Children and adults from whom a CSF specimen was available who had been tested with at least 1 conventional method</td>
<td>Retrospective, selection method not clear</td>
<td>Culture and PCR with discrepancy resolution LDT PCR</td>
<td>Stored up to 2 y after collection</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table 4. Results of Clinical Validity Studies of CNS Panel

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition, %</th>
<th>Clinical Validity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td>1643</td>
<td>1560</td>
<td>Insufficient volume, outside the 7-d window, repeat subject, or invalid FilmArray test.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli K1</em></td>
<td>0.1</td>
<td>100 (34 to 100)</td>
<td>99.9 (99.6 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0.06</td>
<td>100 (NA)</td>
<td>99.9 (99.6 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>0</td>
<td>100 (99.8 to 100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitides</em></td>
<td>0</td>
<td>100 (99.8 to 100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>0.06</td>
<td>0 (NA)</td>
<td>99.9 (99.6 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0.3</td>
<td>100 (51 to 100)</td>
<td>99.2 (98.7 to 99.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>0.2</td>
<td>100 (44 to 100)</td>
<td>99.8 (99.4 to 99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterovirus</em></td>
<td>2.9</td>
<td>96 (86 to 99)</td>
<td>99.5 (99.0 to 99.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus 1</td>
<td>0.1</td>
<td>100 (34 to 100)</td>
<td>99.9 (99.5 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus 2</td>
<td>0.6</td>
<td>100 (72 to 100)</td>
<td>99.9 (99.5 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>1.3</td>
<td>86 (65 to 95)</td>
<td>99.7 (99.3 to 99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human parechovirus</td>
<td>0.6</td>
<td>100 (70 to 100)</td>
<td>99.8 (99.4 to 99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella zostervirus</td>
<td>0.3</td>
<td>100 (51 to 100)</td>
<td>99.8 (99.4 to 99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; CSF: cerebrospinal fluid; LDT: laboratory-developed test; NR: not reported; PCR: polymerase chain reaction.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition, %</th>
<th>Clinical Validity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitivity/Positive % Agreement</td>
<td>Specificity/Negative % Agreement</td>
</tr>
<tr>
<td>C. neoformans/</td>
<td>0.06</td>
<td></td>
<td></td>
<td>100 (NA)</td>
<td>99.7 (99.3 to 99.9)</td>
</tr>
<tr>
<td>C. gattii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanson et al (2016)</td>
<td>342</td>
<td>342</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td>0.3</td>
<td>100 (3 to 100)</td>
<td>100 (98 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli K1</td>
<td>1.5</td>
<td>100 (48 to 100)</td>
<td>100 (97 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>0</td>
<td>NA</td>
<td>100 (98 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>0.3</td>
<td>100 (3 to 100)</td>
<td>100 (98 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>0.9</td>
<td>67 (9 to 99)</td>
<td>99 (95 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>1.5</td>
<td>100 (48 to 100)</td>
<td>99 (96 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td>2.0</td>
<td>57 (18 to 90)</td>
<td>100 (91 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td>11.1</td>
<td>97 (86 to 100)</td>
<td>100 (69 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. simplex virus 1</td>
<td>3.5</td>
<td>93 (66 to 100)</td>
<td>98 (89 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. simplex virus 2</td>
<td>8.5</td>
<td>100 (88 to 100)</td>
<td>100 (82 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>5.6</td>
<td>95 (74 to 100)</td>
<td>100 (93 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human parechovirus</td>
<td>0.3</td>
<td>100 (3 to 100)</td>
<td>100 (93 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>9.4</td>
<td>100 (89 to 100)</td>
<td>100 (79 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td>2.6</td>
<td>64 (35 to 87)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. neoformans/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. gattii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graf et al (2017)</td>
<td>133</td>
<td>133</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (1 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (1 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (28 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95 (82 to 99)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (94 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. simplex virus 1</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 (7 to 93)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. simplex virus 2</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (1 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 (9 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (96 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human parechovirus</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94 (70 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 (95 to 100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<sup>b</sup>Confidence intervals not provided in publication; estimated based on available information.
Table 5. Relevance Gaps of Studies of CNS Panel

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber et al (2016)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>4. Participants not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis</td>
<td>3. Used investigational version of test but varies from marketed version only in that Epstein-Barr virus is not available in the marketed version</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanson et al (2016)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>3. Selection criteria with respect to clinical characteristics not described</td>
<td>3. Used investigational version (see above)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graf et al (2017)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>4. Selection criteria varied for positive and negative samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key</td>
<td>1. Intended use population unclear</td>
<td>1. Classification thresholds not defined</td>
<td>1. Study does not directly assess a key health outcome</td>
<td>1. Follow-up duration not sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determined)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Clinical context for test is unclear</td>
<td>2. Version used unclear</td>
<td>2. Evidence chain or decision model not explicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Study population unclear</td>
<td>3. Not compared with credible reference standard</td>
<td>3. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Study population not representative of intended clinical use</td>
<td>3. Not compared with other tests in use for same purpose</td>
<td>4. Reclassification of diagnostic or risk categories not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Study population is subpopulation of intended use</td>
<td></td>
<td>5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FN: false-negative; FP: false-positive; TN: true negative; TP: true positive.
Table 6. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Completeness of Follow-Up</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hanson et al (2016)</td>
<td>1. Not clear if participants were consecutive</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graf et al (2017)</td>
<td>3. Selection not random or consecutive and varied for positive and negatives</td>
<td>1. Not clear if blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key</td>
<td>1. Selection not described</td>
<td>1. Not blinded to results of index or other comparator tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Selection not random nor consecutive (ie, convenience)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Many tests performed on frozen samples</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Not clear if there were indeterminate samples</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tbody>
</table>
| Section Summary: Central Nervous System Bacterial and Viral Panel

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

Cytomegalovirus

Diagnosis of CMV can be made by culture and/or serologies. However, CMV culture for establishing a diagnosis is limited by the slow growth of CMV and low sensitivity. Serologies provide indirect evidence of current and/or historical infection. A variety of tests to detect CMV DNA have been developed, including but not limited to Hybrid Capture (Digene Corp.), Amplicor
CMV Monitor Tests (Roche Molecular Diagnostics), and TaqMan. The specific techniques used may vary by local availability, but studies have suggested that all provide complementary information.\(^{31,32,33,34,35}\)

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 shown to be effective in reducing the risk of CMV disease, it results in a large number of patients being treated unnecessarily. Therefore, preemptive therapy has become an accepted option, in which antiviral therapy is initiated when a laboratory technique identifies an increasing viral load. Late CMV disease, defined as occurring after 100 days, is also a concern, and viral loads can also be monitored to prompt antiviral therapy.

**Enterovirus**

Amplified DNA probes are available for detecting this group of viruses including the polioviruses, coxsackieviruses, echoviruses, and other enteroviruses. In addition to 3 polioviruses, there are more than 60 types of non-polio enteroviruses that can cause disease in humans. Several Food and Drug Administration-approved test kits are available including the GeneXpert Enterovirus Assay, with sensitivity, specificity, PPV, and NPV of 82.1%, 100%, 100%, and 96.2%, respectively. In this study, molecular assays were superior to viral culture for detecting enterovirus RNA in CSF. GeneXpert Enterovirus Assay showed a high specificity but a lower sensitivity for the detection of enterovirus RNA compared with the reverse transcriptase qPCR assay.\(^{36}\) 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).\(^{37}\)

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.\(^{38}\) Similarly, an observational study (2015) reported that the use of enterovirus PCR testing is associated with reduced hospital stay and reduced antibiotic duration in adults with aseptic meningitis.\(^{39}\)

**Vancomycin-Resistant Enterococcus**

Probes are available for detecting vancomycin resistance of organisms (eg, for *Enterococcus*). These probes can detect vancomycin resistance rapidly and accurately so that appropriate antibiotic selection can be made and infectious precautions, such as isolation, can be instituted.\(^{40,41}\)
Gardnerella vaginalis
A 2006 study evaluated vaginal specimens from 321 symptomatic women analyzed for bacterial vaginosis, using both Gram stain with Nugent criteria and a DNA hybridization test (Affirm VPIII hybridization test). Of the 321 patients, 115 (35.8%) were Gram-positive for bacterial vaginosis, and 126 (39.2%) were negative. A total of 80 (25.0%) patients demonstrated intermediate Gram staining that was also considered negative. The DNA hybridization test detected *Gardnerella vaginalis* in 107 (93.0%) of 115 vaginal specimens positive 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
Clinical Context and Test Purpose
The purpose of nucleic acid-based gastrointestinal pathogen panel is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with signs and/or symptoms of gastrointestinal conditions.

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

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

Patients
The relevant population of interest are individuals with signs and/or symptoms of gastroenteritis and gastrointestinal conditions.

Interventions
The intervention being considered is testing with a nucleic acid-based gastrointestinal pathogen panel.

Comparators
Comparators of interest include no gastrointestinal pathogen-specific testing and culture or nucleic acid-based testing for individual pathogens.

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, symptoms, and change in disease status.

Timing
Though not completely standardized, follow-up for suspected gastroenteritis or gastrointestinal conditions would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.
Setting
Patients with signs and/or symptoms of gastroenteritis and gastrointestinal conditions are actively managed by primary care clinician infectious disease specialists and emergency medicine professionals in an emergency or inpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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

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

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

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

**Hepatitis C**
Diagnostic tests for hepatitis C can be divided into 2 general categories: (1) serologic assays that detect antibody to hepatitis C virus (anti-HCV); and (2) molecular assays that detect, quantify, and/or characterize 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**
**Clinical Context and Test Purpose**
The purpose of nucleic acid probe for hepatitis G is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with hepatitis.

The question addressed in this evidence review is: does testing for microorganisms using nucleic acid probes improve the net health outcome in individuals with suspected hepatitis G infection?

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

**Patients**
The relevant population of interest are individuals with hepatitis.

**Interventions**
The intervention being considered is testing with a nucleic acid probe for hepatitis G.

**Comparators**
Comparators of interest include no hepatitis G-specific testing and serologic assays to detect antibodies.

**Outcomes**
The general outcomes of interest are test accuracy, test validity, other test performance measures, symptoms, and change in disease status.

**Timing**
Though not completely standardized, follow-up for suspected hepatitis G would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.

**Setting**
Patients with hepatitis are actively managed by primary care providers or infectious disease specialists in an outpatient clinical setting.
Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

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

Herpes Simplex Virus
Typing of HSV isolates is required to identify the virus isolated in culture. The methods available for this include antigen detection by immunofluorescence (IF) assays and PCR. A 2009 cross-sectional study used 4 reference strains and 42 HSV isolates obtained from patients between September 1998 and September 2004.52 These isolates were subjected to testing using a MAb-based IF test and a PCR that detects the polymerase (pol) gene of HSV isolates. The observed agreement of the MAb IF assay with the PCR was 95.7%. A total of 54.8% (23/42) of isolates tested by IF typing were found to be HSV-1, 40.5% (17/42) were HSV-2, and 2 (4.8%) were untypable using the MAb IF assay. The 2 untypable isolates were found to be HSV-2 using the pol PCR. According to the American Academy of Family Physicians, antiviral medications have expanded treatment options for the 2 most common cutaneous manifestations, HSV-1 and HSV-2. Acyclovir therapy remains an effective option; however, famciclovir and valacyclovir offer improved oral bioavailability and convenient oral dosing schedules but at a higher cost. Patients who have 6 or more recurrences of genital herpes per year can be treated with daily regimens, which are effective in suppressing 70% to 80% of symptomatic recurrences.

Human Herpesvirus 6
Human herpesvirus 6 (HHV-6) can be detected with a number of immunoassays. The high rate of seropositivity in the general population makes interpreting positive results difficult. Historically, paired samples with a rise in antibody titer have been needed to diagnose an active infection. Qualitative and quantitative PCR tests are available for HHV-6 in blood and other samples. At least 1 evaluation (2014) of rt-PCR detecting viral mRNA transcripts in hematopoietic cell transplant subjects showed good analytic validity.53

Most often, in healthy patients, HHV-6 causes no symptoms or a mild-self-limited illness. In these cases, a definitive diagnosis of HHV-6 has little utility. However, the primary HHV-6 infection can cause severe disease including thrombocytopenia, hepatitis, myocarditis, and meningoencephalitis. In immunosuppressed patients, particularly hematopoietic cell transplant
recipients, HHV-6 reactivation may cause a range of severe symptoms. A number of antiviral agents are active against HHV-6 (eg, ganciclovir, foscarnet). A variety of treatment strategies are used for immunosuppressed patients, which can be classified as prophylactic (all at-risk patients treated), preemptive (patients treated when viral replication is detected), and curative (patients treated when the disease is confirmed). The use of a quantitative HHV-6 assay may be used in treatment-related decisions.

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

**Human Immunodeficiency Virus 2**
DNA probes are available for diagnosis and quantification of HIV-2. HIV-2 is most commonly found in Western Africa, although it has been reported in the United States. Blood donations are routinely tested for HIV-2, but clinical testing for HIV-2 is typically limited to those in contact with persons in a country where HIV-2 is endemic or when clinical evaluation suggests HIV infection, but testing for Human Immunodeficiency Virus1 is negative. HIV-2 quantification is regularly done to determine viral load in infected patients to monitor response to antiretroviral therapies.

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

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

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

DNA probes for *Legionella pneumophila* have been developed. A 2010 study compared the usefulness of 2 rt-PCR assays (qrt-PCR*mip* targeting *L. pneumophila* and qrt-PCR16S targeting all *Legionella* species) performed on lower respiratory tract samples for diagnostic and prognostic purposes in 311 patients hospitalized for community-acquired pneumonia. The Now Legionella urinary antigen test from Binax (Portland, ME) was used as a reference test. One subset of 255 community-acquired pneumonia patients admitted to a single hospital in 2005 and 2006 were evaluated, and the sensitivities, specificities, PPVs, and NPVs for both rt-PCR tests were 63.6%, 98.7%, 77.7%, and 97.4%, respectively. Diederen et al (2008) evaluated the use of a rt-PCR assay for *Legionella* species in 151 subjects with respiratory infections, 37 (25%) of whom fulfilled the European Working Group for Legionella Infections criteria for *Legionella* pneumonia and were considered to have *Legionella* pneumonia. For a 16S rRNA-based PCR, the estimated sensitivity and specificity were 86% (95% CI, 72% to 95%) and 95% (95% CI, 90% to 98%), respectively. For a *mip* gene-based PCR, the estimated sensitivity and specificity were 92% (95% CI, 78% to 98%) and 98% (95% CI, 93% to 100%), respectively. Another study (2012) reported a significantly higher sensitivity for PCR vs culture in detecting *L. pneumophila* in samples taken within 2 days or less of hospitalization (94.7% vs 79.6%, respectively) or 3 to 14 days of hospitalization (79.3% and 47.8%, respectively).

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

**Mycobacteria Species**

DNA probes are available to distinguish between *Mycobacterium* species. In a 2012 study, the extracted DNA specimens from *Mycobacterium* species and non-mycobacterial species were tested using peptide nucleic acid probe-based rt-PCR assay to evaluate potential cross-reactivity. A total of 531 respiratory specimens (482 sputum specimens, 49 bronchoalveolar washing fluid specimens) were collected from 230 patients in July and August 2011. All specimens were analyzed for *Mycobacteria* by direct smear examination, mycobacterial culture, and peptide nucleic acid probe-based rt-PCR assay. In cross-reactivity tests, no false-positive or false-negative results were evident. When the culture method was used as the criterion standard test for comparison, peptide nucleic acid probe-based rt-PCR assay for detection of *Mycobacterium tuberculosis* complex (MTBC) had a sensitivity and specificity of 96.7% (58/60) and 99.6% (469/471), respectively. Assuming the combination of culture and clinical diagnosis as the standard, the sensitivity and specificity of the rt-PCR assay for detection of MTBC were 90.6% (58/64) and 99.6% (465/467), respectively. The new rt-PCR for the detection of nontuberculous mycobacteria had a sensitivity and specificity of 69.0% (29/42) and 100% (489/489), respectively.

**Mycobacterium tuberculosis**

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

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

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

In many cases, management of *M. pneumoniae* infection does not require definitive diagnosis (eg, community-acquired pneumonia). However, there are some cases where *M. pneumoniae* is associated with severe illnesses that can have a variety of causes, in which definitive diagnosis may make a difference in treatment. *M. pneumoniae* PCR can be used to detect *M. pneumoniae* in patients with Stevens-Johnson syndrome, and refractory/severe pneumonia. At least 1 study (2014) has suggested that inappropriate antibiotic use may worsen fulminant mycoplasma infection, and patients benefit from early administration of appropriate antimycoplasmal drugs with steroids.

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

**Respiratory Viral Panel**

A broad spectrum of pathogens is causative for respiratory tract infections, but symptoms are mostly similar. The identification of the causative viruses is only feasible using multiplex PCR or several monoplex PCR tests in parallel. Several studies of various respiratory viral panels have demonstrated the multiplex assay detected clinically important viral infections in a single genomic test and thus, may be useful for detecting causative agents for respiratory tract disorders. 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.77,78,79 A 2011 randomized study by Brittain-Long et al, which assessed 406 patients with access to a rapid, multiplex PCR assay used to detect 13 viruses, reported lower antibiotic prescription rates (4.5% vs 12.3%, respectively) vs delayed identification with no significant difference in outcomes at follow-up (p=0.359).80 Access to a rapid method for etiologic diagnosis of respiratory tract infections might reduce antibiotic prescription rates at the initial visit in an outpatient setting.

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

Probes are available for the detection of *Staphylococcus aureus*.81,82 These probes not only distinguish between coagulase-negative *Staphylococcus* and *S. aureus*, but they can also detect methicillin-resistant species with high accuracy.41,42 Given the importance of establishing an early and accurate diagnosis in clinical situations in which an *S. aureus* infection is likely, and there is a substantial likelihood of methicillin-resistant species, there is a clinical utility for testing in these situations.

**Streptococcus, Group A**

While group A *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) can cause a variety of clinical symptoms including impetigo, pharyngitis, and more invasive infections (eg, necrotizing fasciitis, pneumonia), most of the focus of rapid detection methods is on the diagnosis of GAS pharyngitis. Patients with confirmed acute GAS pharyngitis are typically treated with antibiotics, which shorten the duration of symptoms modestly and help prevent acute rheumatic fever. The diagnosis of GAS pharyngitis can be made by culture, which has a sensitivity of 90% to 95% but is limited by a slow turnaround time (1-2 days), which may hamper decisions about initiating antibiotic therapy. Point-of-care rapid antigen detection tests are widely used to diagnose GAS pharyngitis. Point-of-care rapid antigen detection tests are characterized by high specificity (~95%) but poor sensitivity (70%-90%) compared with culture.83

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

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen-Probe Group A</td>
<td>Gen-Probe, San Diego, CA (Hologic)</td>
<td>Nonamplified</td>
</tr>
<tr>
<td><em>Streptococcus</em> Direct Test</td>
<td></td>
<td>Sensitivity of 91.7%, specificity of 99.3%, and overall agreement of 97.4% vs culture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Turnaround time of 60 min</td>
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</tbody>
</table>


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

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

<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 (2016)</td>
<td>Illumigene GAS assay</td>
<td>757 pharyngeal swabs from school-based setting (12.2% GAS culture-positive)</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>
<tr>
<td>Cohen et al (2015)</td>
<td>Alere i Strep A assay</td>
<td>481 pharyngeal swabs (30.4% GAS culture-positive)</td>
<td>95.9 (92.7 to 99.1) (98.7 after discrepant analysis)</td>
<td>94.6 (92.2 to 97.0) (98.5 after discrepant analysis)</td>
<td>88.7 (83.8 to 93.6) (96.9 after discrepant analysis)</td>
<td>98.1 (96.7 to 99.6) (99.4 after discrepant analysis)</td>
</tr>
<tr>
<td>Faron et al (2015)</td>
<td>AmpliVue GAS assay</td>
<td>1192 pharyngeal swabs (14.5% GAS culture-positive)</td>
<td>98.3 (95 to 100)</td>
<td>93.2 (91 to 95)</td>
<td>71.2</td>
<td>99.7</td>
</tr>
<tr>
<td>Boyanton et al (2016)</td>
<td>Lyra Direct Strep assay</td>
<td>161 pharyngeal swabs from patients with negative RADTs</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

CI: confidence interval; GAS: group A Streptococcus; NPV: negative predictive value; NR: not reported; PCR: polymerase chain reaction; PPV: positive predictive value; RADT: rapid antigen detection test.
In most studies of the amplified PCR assays, the sensitivity and specificity of the probes are very high. Upton et al (2016) reported lower sensitivity and lowered PPV for the Illumigene assay than previous studies using this assay.\(^9^0\) The authors hypothesized that the lower PPV might have been related to the fact that the study was conducted in a population of children attending school, lowering the pretest probability of actual GAS infection. Alternatively, the PCR assay might be detecting isolates of other Streptococcus species that carry the GAS pyrogenic exotoxin B gene, which is detected by the assay.

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

**Streptococcus, Group B**

Several rapid PCR-based tests for group B Streptococcus (GBS) have been developed, with reported sensitivities and specificities similar to those of conventional culture. DNA probes have also been developed to identify GBS from cultured specimens.\(^9^4,9^5\) 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 (2009) compared the performance characteristics of PCR testing for Trichomonas with wet prep microscopy and culture in 296 female and 298 male subjects.\(^9^6\) In both women and men, DNA probe testing of vaginal swabs was more sensitive than culture. However, in men, wet prep testing was more sensitive than DNA probe testing. Munson et al (2010) compared DNA probe testing with culture in 255 vaginal saline preparations.\(^9^7\) The DNA probe identified Trichomonas in 9.4% (24/255) of specimens that were negative on culture. This probe offers the ability to better distinguish between causes of vaginitis, which can be difficult to assess clinically and the obviate the use of standard culture methods. Nucleic acid amplification tests have demonstrated higher clinical sensitivity than culture and wet mount microscopy, as well as single-probe nonamplified testing in general.\(^9^6\) A 2011 prospective multicenter study of 1025 asymptomatic and symptomatic women found nucleic acid amplification testing had a clinical sensitivity of 100% for both vaginal and endocervical swabs while urine specimen sensitivity was 95.2%.\(^9^8\) Specificity rates ranged from 98.9% to 99.6%. Other studies have also reported similar results.\(^9^9\) PCR amplification tests have higher clinical sensitivity and are considered the standard of care for diagnosing Trichomonas vaginalis when culturing is not an option.

**Summary of Evidence**

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

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

For individuals who have signs and/or symptoms of gastroenteritis who receive nucleic acid-based gastrointestinal pathogen panel, the evidence includes prospective and retrospective evaluations of the tests’ sensitivity and specificity. Relevant outcomes include test accuracy and validity, other test performance measures, symptoms, and change in disease status. The evidence suggests that gastrointestinal pathogen panels are likely to identify both bacterial and viral pathogens with high sensitivity, compared with standard methods. Access to a rapid method for etiologic diagnosis of gastrointestinal infections may lead to more effective early treatment and infection-control measures. However, in most instances, when a specific pathogen is suspected, individual tests could be ordered. There may be a subset of patients with an unusual presentation who would warrant testing for a panel of pathogens at once, but that subset has not been well defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For other nucleic acid probes discussed in this review, the tests’ clinical utility was evaluated based on whether there is demonstrated clinical validity, along with either direct evidence of improved outcomes or a chain of evidence indicating that changes in management leading to improved outcomes are likely to occur with testing. For example, for group A Streptococcus, use of nucleic acid-based testing can result in a reduction in antibiotic use as a result of not needing to initiate empirical antibiotics pending culture results. In many cases, clinical input has 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 posttransplant setting).

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
In response to requests, input was received from 2 academic medical centers and 4 specialty societies while this policy was under review in 2015. Input was characterized by a number of nonresponses, making it difficult to assess for consensus across reviewers for some infectious agents. However, there was clear agreement (support from all reviewers who responded to that question) in support of nucleic acid probes for *Bartonella* species, *Candida* species, *Chlamydia trachomatis*, *Clostridium difficile*, cytomegalovirus, *Enterococcus faecalis*, vancomycin-resistant *Enterococcus*, enterovirus, *Gardnerella vaginalis*, hepatitis B and C viruses, herpes simplex virus, human herpesvirus 6, HIV-1 and -2, human papillomavirus, influenza virus, *Mycobacteria* species, *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*, *Neisseria gonorrhoeae*, respiratory viruses, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, group B Streptococcus, and *Trichomonas vaginalis*.

**Practice Guidelines and Position Statements**
No guidelines or statements were identified.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in October 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**CODING**
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) 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 of these services as it applies to an individual member.

**CPT/HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>87471</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); <em>Bartonella henselae</em> and <em>Bartonella quintana</em>, amplified probe technique</td>
</tr>
<tr>
<td>87472</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); <em>Bartonella henselae</em> and <em>Bartonella quintana</em>, quantification</td>
</tr>
<tr>
<td>87480</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); <em>Candida</em> species, direct probe technique</td>
</tr>
<tr>
<td>87481</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); <em>Candida</em> species, amplified probe technique</td>
</tr>
<tr>
<td>87482</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); <em>Candida</em> species, quantification</td>
</tr>
<tr>
<td>87483</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); central nervous system pathogen (eg, <em>Neisseria meningitidis</em>, <em>Streptococcus pneumoniae</em>, <em>Listeria</em>, <em>Haemophilus influenzae</em>, <em>E. coli</em>, <em>Streptococcus agalactiae</em>, enterovirus, human parechovirus, herpes simplex virus type 1 and 2, human herpesvirus 6, cytomegalovirus, varicella zoster virus, <em>Cryptococcus</em>), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets</td>
</tr>
</tbody>
</table>
87485 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, direct probe technique
87486 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, amplified probe technique
87487 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, quantification
87490 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique
87491 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
87492 Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, quantification
87493 Infectious agent detection by nucleic acid (DNA or RNA); Clostridium difficile, toxin gene(s), amplified probe technique
87495 Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, direct probe technique
87496 Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique
87497 Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, quantification
87498 Infectious agent detection by nucleic acid (DNA or RNA); enterovirus, amplified probe technique, includes reverse transcription when performed
87500 Infectious agent detection by nucleic acid (DNA or RNA); vancomycin resistance (eg, enterococcus species van A, van B), amplified probe technique
87505 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
87506 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
87507 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
87510 Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, direct probe technique
87511 Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, amplified probe technique
87512 Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification
87516 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, amplified probe technique
87517 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, quantification
87520 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique
87521 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, amplified probe technique, includes reverse transcription when performed
87522 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, quantification, includes reverse transcription when performed
87525 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, direct probe technique
87526 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, amplified probe technique
87527 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, quantification
87528 Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, direct probe technique
87529 Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, amplified probe technique
87530 Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, quantification
87531 Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, direct probe technique
87532 Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, amplified probe technique
87533 Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, quantification
87534 Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, direct probe technique
87535 Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, amplified probe technique, includes reverse transcription when performed
87536 Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed
87537 Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, direct probe technique
87538 Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, amplified probe technique, includes reverse transcription when performed
87539 Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, quantification, includes reverse transcription when performed
87540 Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, direct probe technique
87541 Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, amplified probe technique
87542 Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, quantification
87550 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, direct probe technique
87551 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, amplified probe technique
87552 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, quantification
87555 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, direct probe technique
87556 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, amplified probe technique
87557 Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, quantification
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus,</td>
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<td>Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus,</td>
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87653 Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group B, amplified probe technique
87660 Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique
87661 User Defined (description not available)
87797 Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
87798 Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
87799 Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
0096U Human papillomavirus (HPV), high-risk types (ie, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), male urine [Test name- HPV, High-Risk, Male Urine; Manufacturer—Molecular Testing Lab]
0097U Gastrointestinal pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes [Test name- BioFire® FilmArray® Gastrointestinal (GI) Panel; Manufacturer—BioFire® Diagnostics]
0098U Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes [Test name- BioFire® FilmArray® Gastrointestinal (GI) Panel; Manufacturer—BioFire® Diagnostics]
0099U Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes [Test name- BioFire® FilmArray® Respiratory Panel (RP); Manufacturer—BioFire® Diagnostics]
0100U Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes [Test name- BioFire® FilmArray® Respiratory Panel 2 (RP2); Manufacturer—BioFire® Diagnostics]
0115U Respiratory infectious agent detection by nucleic acid (DNA and RNA), 18 viral types and subtypes and two bacterial targets, amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected.

- 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.

**ICD-10 Diagnoses** (Effective October 1, 2015)

- A04.71 Enterocolitis due to Clostridium difficile, recurrent
- A04.72 Enterocolitis due to Clostridium difficile, not specified as recurrent
- A15.0 Tuberculosis of lung
- A15.4 Tuberculosis of intrathoracic lymph nodes
- A15.5 Tuberculosis of larynx, trachea and bronchus
- A15.6 Tuberculous pleurisy
- A15.7 Primary respiratory tuberculosis
- A15.8 Other respiratory tuberculosis
- A15.9 Respiratory tuberculosis unspecified
- A17.0 Tuberculous meningitis
- A17.1 Meningeal tuberculoma
- A17.81 Tuberculoma of brain and spinal cord
A17.82 Tuberculous meningoencephalitis
A17.83 Tuberculous neuritis
A17.89 Other tuberculosis of nervous system
A17.9 Tuberculosis of nervous system, unspecified
A18.01 Tuberculosis of spine
A18.02 Tuberculous arthritis of other joints
A18.03 Tuberculosis of other bones
A18.09 Other musculoskeletal tuberculosis
A18.10 Tuberculosis of genitourinary system, unspecified
A18.11 Tuberculosis of kidney and ureter
A18.12 Tuberculosis of bladder
A18.13 Tuberculosis of other urinary organs
A18.14 Tuberculosis of prostate
A18.15 Tuberculosis of other male genital organs
A18.16 Tuberculosis of cervix
A18.17 Tuberculous female pelvic inflammatory disease
A18.18 Tuberculosis of other female genital organs
A18.2 Tuberculosis peripheral lymphadenopathy
A18.31 Tuberculous peritonitis
A18.32 Tuberculous enteritis
A18.39 Retroperitoneal tuberculosis
A18.4 Tuberculosis of skin and subcutaneous tissue
A18.50 Tuberculosis of eye, unspecified
A18.51 Tuberculous episcleritis
A18.52 Tuberculous keratitis
A18.53 Tuberculous chorioretinitis
A18.54 Tuberculous iridocyclitis
A18.59 Other tuberculosis of eye
A18.6 Tuberculosis of (inner) (middle) ear
A18.7 Tuberculosis of adrenal glands
A18.81 Tuberculosis of thyroid gland
A18.82 Tuberculosis of other endocrine glands
A18.83 Tuberculosis of digestive tract organs, not elsewhere classified
A18.84 Tuberculosis of heart
A18.85 Tuberculosis of spleen
A18.89 Tuberculosis of other sites
A19.0 Acute miliary tuberculosis of a single specified site
A19.1 Acute miliary tuberculosis of multiple sites
A19.2 Acute miliary tuberculosis, unspecified
A19.8 Other miliary tuberculosis
A19.9 Miliary tuberculosis, unspecified
A21.0 Ulceroglandular tularemia
A21.1 Oculoglandular tularemia
A21.2 Pulmonary tularemia
A21.3 Gastrointestinal tularemia
A21.7 Generalized tularemia
A21.8 Other forms of tularemia
A21.9 Tularemia, unspecified
A23.0 Brucellosis due to Brucella melitensis
A23.1 Brucellosis due to Brucella abortus
A23.2 Brucellosis due to Brucella suis
A23.3 Brucellosis due to Brucella canis
A23.8 Other brucellosis
A23.9  Brucellosis, unspecified
A24.1  Acute and fulminating melioidosis
A24.2  Subacute and chronic melioidosis
A24.3  Other melioidosis
A24.9  Melioidosis, unspecified
A28.1  Cat-scratch disease
A30.0  Indeterminate leprosy
A30.1  Tuberculoid leprosy
A30.2  Borderline tuberculoid leprosy
A30.3  Borderline leprosy
A30.4  Borderline lepromatous leprosy
A30.5  Lepromatous leprosy
A30.8  Other forms of leprosy
A30.9  Leprosy, unspecified
A31.0  Pulmonary mycobacterial infection
A31.1  Cutaneous mycobacterial infection
A31.2  Disseminated mycobacterium avium-intracellulare complex (DMAC)
A31.8  Other mycobacterial infections
A31.9  Mycobacterial infection, unspecified
A37.00  Whooping cough due to Bordetella pertussis without pneumonia
A37.01  Whooping cough due to Bordetella pertussis with pneumonia
A37.10  Whooping cough due to Bordetella parapertussis without pneumonia
A37.11  Whooping cough due to Bordetella parapertussis with pneumonia
A37.80  Whooping cough due to other Bordetella species without pneumonia
A37.81  Whooping cough due to other Bordetella species with pneumonia
A37.90  Whooping cough, unspecified species without pneumonia
A37.91  Whooping cough, unspecified species with pneumonia
A39.0  Meningococcal meningitis
A41.02  Sepsis due to Methicillin resistant Staphylococcus aureus
A44.0  Systemic bartonellosis
A44.1  Cutaneous and mucocutaneous bartonellosis
A44.8  Other forms of bartonellosis
A44.9  Bartonellosis, unspecified
A48.1  Legionnaires' disease
A48.2  Nonpneumonic Legionnaires' disease [Pontiac fever]
A49.02  Methicillin resistant Staphylococcus aureus infection, unspecified site
A49.3  Mycoplasma infection, unspecified site
A50.01  Early congenital syphilitic oculopathy
A50.02  Early congenital syphilitic osteochondropathy
A50.03  Early congenital syphilitic pharyngitis
A50.04  Early congenital syphilitic pneumonia
A50.05  Early congenital syphilitic rhinitis
A50.06  Early cutaneous congenital syphilis
A50.07  Early mucocutaneous congenital syphilis
A50.08  Early visceral congenital syphilis
A50.09  Other early congenital syphilis, symptomatic
A50.1  Early congenital syphilis, latent
A50.2  Early congenital syphilis, unspecified
A50.30  Late congenital syphilitic oculopathy, unspecified
A50.31  Late congenital syphilitic interstitial keratitis
A50.32  Late congenital syphilitic chorioretinitis
A50.39  Other late congenital syphilitic oculopathy
A50.40  Late congenital neurosyphilis, unspecified
A50.41 Late congenital syphilitic meningitis
A50.42 Late congenital syphilitic encephalitis
A50.43 Late congenital syphilitic polyneuropathy
A50.44 Late congenital syphilitic optic nerve atrophy
A50.45 Juvenile general paresis
A50.49 Other late congenital neurosyphilis
A50.51 Clutton's joints
A50.52 Hutchinson's teeth
A50.53 Hutchinson's triad
A50.54 Late congenital cardiovascular syphilis
A50.55 Late congenital syphilitic arthropathy
A50.56 Late congenital syphilitic osteochondropathy
A50.57 Syphilitic saddle nose
A50.59 Other late congenital syphilis, symptomatic
A50.6 Late congenital syphilis, latent
A50.7 Late congenital syphilis, unspecified
A50.9 Congenital syphilis, unspecified
A51.0 Primary genital syphilis
A51.1 Primary anal syphilis
A51.2 Primary syphilis of other sites
A51.31 Condyloma latum
A51.32 Syphilitic alopecia
A51.39 Other secondary syphilis of skin
A51.41 Secondary syphilitic meningitis
A51.42 Secondary syphilitic female pelvic disease
A51.43 Secondary syphilitic oculopathy
A51.44 Secondary syphilitic nephritis
A51.45 Secondary syphilitic hepatitis
A51.46 Secondary syphilitic osteopathy
A51.49 Other secondary syphilitic conditions
A51.5 Early syphilis, latent
A51.9 Early syphilis, unspecified
A52.00 Cardiovascular syphilis, unspecified
A52.01 Syphilitic aneurysm of aorta
A52.02 Syphilitic aortitis
A52.03 Syphilitic endocarditis
A52.04 Syphilitic cerebral arteritis
A52.05 Other cerebrovascular syphilis
A52.06 Other syphilitic heart involvement
A52.09 Other cardiovascular syphilis
A52.10 Symptomatic neurosyphilis, unspecified
A52.11 Tabes dorsalis
A52.12 Other cerebrospinal syphilis
A52.13 Late syphilitic meningitis
A52.14 Late syphilitic encephalitis
A52.15 Late syphilitic neuropathy
A52.16 Charcot's arthropathy (tabetic)
A52.17 General paresis
A52.19 Other symptomatic neurosyphilis
A52.2 Asymptomatic neurosyphilis
A52.3 Neurosyphilis, unspecified
A52.71 Late syphilitic oculopathy
A52.72 Syphilis of lung and bronchus
A52.73  Symptomatic late syphilis of other respiratory organs
A52.74  Syphilis of liver and other viscera
A52.75  Syphilis of kidney and ureter
A52.76  Other genitourinary symptomatic late syphilis
A52.77  Syphilis of bone and joint
A52.78  Syphilis of other musculoskeletal tissue
A52.79  Other symptomatic late syphilis
A52.8  Late syphilis, latent
A52.9  Late syphilis, unspecified
A53.0  Latent syphilis, unspecified as early or late
A53.9  Syphilis, unspecified
A54.00  Gonococcal infection of lower genitourinary tract, unspecified
A54.01  Gonococcal cystitis and urethritis, unspecified
A54.02  Gonococcal vulvovaginitis, unspecified
A54.03  Gonococcal cervicitis, unspecified
A54.09  Other gonococcal infection of lower genitourinary tract
A54.1  Gonococcal infection of lower genitourinary tract with periurethral and accessory gland abscess
A54.21  Gonococcal infection of kidney and ureter
A54.22  Gonococcal prostatitis
A54.23  Gonococcal infection of other male genital organs
A54.24  Gonococcal female pelvic inflammatory disease
A54.29  Other gonococcal genitourinary infections
A54.30  Gonococcal infection of eye, unspecified
A54.31  Gonococcal conjunctivitis
A54.32  Gonococcal iridocyclitis
A54.33  Gonococcal keratitis
A54.39  Other gonococcal eye infection
A54.40  Gonococcal infection of musculoskeletal system, unspecified
A54.41  Gonococcal spondylolpathy
A54.42  Gonococcal arthritis
A54.43  Gonococcal osteomyelitis
A54.49  Gonococcal infection of other musculoskeletal tissue
A54.5  Gonococcal pharyngitis
A54.6  Gonococcal infection of anus and rectum
A54.81  Gonococcal meningitis
A54.82  Gonococcal brain abscess
A54.83  Gonococcal heart infection
A54.84  Gonococcal pneumonia
A54.85  Gonococcal peritonitis
A54.86  Gonococcal sepsis
A54.89  Other gonococcal infections
A54.9  Gonococcal infection, unspecified
A55  Chlamydial lymphogranuloma (venereum)
A57  Chancroid
A59.00  Urogenital trichomoniasis, unspecified
A59.01  Trichomonal vulvovaginitis
A59.02  Trichomonal prostatitis
A59.03  Trichomonal cystitis and urethritis
A59.09  Other urogenital trichomoniasis
A59.8  Trichomoniasis of other sites
A59.9  Trichomoniasis, unspecified
A60.00  Herpesviral infection of urogenital system, unspecified
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<td>Herpesviral cervicitis</td>
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<td>Epidemic louse-borne typhus fever due to Rickettsia prowazekii</td>
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<td>Typhus fever due to Rickettsia typhi</td>
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<td>Ehrlichiosis chafeensis [E. chafeensis]</td>
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<td>West Nile virus infection with other neurologic manifestation</td>
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<td>A92.39</td>
<td>West Nile virus infection with other complications</td>
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<td>A92.4</td>
<td>Rift Valley fever</td>
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<td>A92.8</td>
<td>Other specified mosquito-borne viral fevers</td>
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<td>A93.0</td>
<td>Oropouche virus disease</td>
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<td>Colorado tick fever</td>
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<td>A98.0</td>
<td>Crimean-Congo hemorrhagic fever</td>
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<td>B0.0</td>
<td>Eczema herpeticum</td>
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<td>B0.1</td>
<td>Herpesviral vesicular dermatitis</td>
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<td>B0.2</td>
<td>Herpesviral gingivostomatitis and pharyngotonsillitis</td>
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<td>B0.3</td>
<td>Herpesviral meningitis</td>
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<td>B0.4</td>
<td>Herpesviral encephalitis</td>
</tr>
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<td>B0.50</td>
<td>Herpesviral ocular disease, unspecified</td>
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<tr>
<td>B0.51</td>
<td>Herpesviral iridocyclitis</td>
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<td>B0.52</td>
<td>Herpesviral keratitis</td>
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</table>
B00.53 Herpesviral conjunctivitis
B00.59 Other herpesviral disease of eye
B00.7 Disseminated herpesviral disease
B00.81 Herpesviral hepatitis
B00.82 Herpes simplex myelitis
B00.89 Other herpesviral infection
B00.9 Herpesviral infection, unspecified
B01.0 Varicella meningitis
B01.11 Varicella encephalitis and encephalomyelitis
B01.12 Varicella myelitis
B01.2 Varicella pneumonia
B01.81 Varicella keratitis
B01.89 Other varicella complications
B01.9 Varicella without complication
B02.0 Zoster encephalitis
B02.1 Zoster meningitis
B02.21 Postherpetic geniculate ganglionitis
B02.22 Postherpetic trigeminal neuralgia
B02.23 Postherpetic polyneuropathy
B02.24 Postherpetic myelitis
B02.29 Other postherpetic nervous system involvement
B02.30 Zoster ocular disease, unspecified
B02.31 Zoster conjunctivitis
B02.32 Zoster iridocyclitis
B02.33 Zoster keratitis
B02.34 Zoster scleritis
B02.39 Other herpes zoster eye disease
B02.7 Disseminated zoster
B02.8 Zoster with other complications
B02.9 Zoster without complications
B05.0 Measles complicated by encephalitis
B05.1 Measles complicated by meningitis
B05.2 Measles complicated by pneumonia
B05.3 Measles complicated by otitis media
B05.4 Measles with intestinal complications
B05.81 Measles keratitis and keratoconjunctivitis
B05.89 Other measles complications
B05.9 Measles without complication
B08.21 Exanthema subitum [sixth disease] due to human herpesvirus 6
B08.3 Erythema infectiosum [fifth disease]
B10.01 Human herpesvirus 6 encephalitis
B10.81 Human herpesvirus 6 infection
B16.0 Acute hepatitis B with delta-agent with hepatic coma
B16.1 Acute hepatitis B with delta-agent without hepatic coma
B16.2 Acute hepatitis B without delta-agent with hepatic coma
B16.9 Acute hepatitis B without delta-agent and without hepatic coma
B17.10 Acute hepatitis C with hepatic coma
B17.11 Acute hepatitis C with hepatic coma
B18.0 Chronic viral hepatitis B with delta-agent
B18.1 Chronic viral hepatitis B without delta-agent
B18.2 Chronic viral hepatitis C
B19.10 Unspecified viral hepatitis B without hepatic coma
B19.11 Unspecified viral hepatitis B with hepatic coma
B19.20 Unspecified viral hepatitis C without hepatic coma
B19.21 Unspecified viral hepatitis C with hepatic coma
B20 Human immunodeficiency virus [HIV] disease
B25.0 Cytomegaloviral pneumonitis
B25.1 Cytomegaloviral hepatitis
B25.2 Cytomegaloviral pancreatitis
B25.8 Other cytomegaloviral diseases
B25.9 Cytomegaloviral disease, unspecified
B26.0 Mumps orchitis
B26.1 Mumps meningitis
B26.2 Mumps encephalitis
B26.3 Mumps pancreatitis
B26.81 Mumps hepatitis
B26.82 Mumps myocarditis
B26.83 Mumps nephritis
B26.84 Mumps polyneuropathy
B26.85 Mumps arthritis
B26.89 Other mumps complications
B26.9 Mumps without complication
B33.1 Ross River disease
B33.3 Retrovirus infections, not elsewhere classified
B33.8 Other specified viral diseases
B34.0 Adenovirus infection, unspecified
B34.1 Enterovirus infection, unspecified
B34.2 Coronavirus infection, unspecified
B34.3 Parvovirus infection, unspecified
B34.4 Papovavirus infection, unspecified
B34.8 Other viral infections of unspecified site
B50.0 Plasmodium falciparum malaria with cerebral complications
B50.8 Other severe and complicated Plasmodium falciparum malaria
B50.9 Plasmodium falciparum malaria, unspecified
B51.0 Plasmodium vivax malaria with rupture of spleen
B51.8 Plasmodium vivax malaria with other complications
B51.9 Plasmodium vivax malaria without complication
B52.0 Plasmodium malariae malaria with nephropathy
B52.8 Plasmodium malariae malaria with other complications
B52.9 Plasmodium malariae malaria without complication
B53.0 Plasmodium ovale malaria
B53.1 Malaria due to simian plasmodia
B53.8 Other malaria, not elsewhere classified
B54 Unspecified malaria
B55.0 Visceral leishmaniasis
B55.1 Cutaneous leishmaniasis
B55.2 Mucocutaneous leishmaniasis
B55.9 Leishmaniasis, unspecified
B58.00 Toxoplasma oculopathy, unspecified
B58.01 Toxoplasma chorioretinitis
B58.09 Other toxoplasma oculopathy
B58.1 Toxoplasma hepatitis
B58.2 Toxoplasma meningoencephalitis
B58.3 Pulmonary toxoplasmosis
B58.81 Toxoplasma myocarditis
B58.82 Toxoplasma myositis
B58.83  Toxoplasma tubulo-interstitial nephropathy
B58.89  Toxoplasmosis with other organ involvement
B58.9  Toxoplasmosis, unspecified
B60.0  Babesiosis
B95.1  Streptococcus, group B, as the cause of diseases classified elsewhere
B95.62  Methicillin resistant Staphylococcus aureus infection as the cause of diseases classified elsewhere
B96.0  Mycoplasma pneumoniae [M. pneumoniae] as the cause of diseases classified elsewhere
B96.81  Helicobacter pylori [H. pylori] as the cause of diseases classified elsewhere
B96.82  Vibrio vulnificus as the cause of diseases classified elsewhere
B96.89  Other specified bacterial agents as the cause of diseases classified elsewhere
B97.0  Adenovirus as the cause of diseases classified elsewhere
B97.11  Coxsackievirus as the cause of diseases classified elsewhere
B97.12  Echovirus as the cause of diseases classified elsewhere
B97.19  Other enterovirus as the cause of diseases classified elsewhere
B97.21  SARS-associated coronavirus as the cause of diseases classified elsewhere
B97.29  Other coronavirus as the cause of diseases classified elsewhere
B97.30  Unspecified retrovirus as the cause of diseases classified elsewhere
B97.31  Lentivirus as the cause of diseases classified elsewhere
B97.32  Oncovirus as the cause of diseases classified elsewhere
B97.33  Human T-cell lymphotrophic virus, type I [HTLV-I] as the cause of diseases classified elsewhere
B97.34  Human T-cell lymphotrophic virus, type II [HTLV-II] as the cause of diseases classified elsewhere
B97.35  Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere
B97.39  Other retrovirus as the cause of diseases classified elsewhere
B97.5  Reovirus as the cause of diseases classified elsewhere
B97.6  Parvovirus as the cause of diseases classified elsewhere
B97.81  Human metapneumovirus as the cause of diseases classified elsewhere
B97.89  Other viral agents as the cause of diseases classified elsewhere
D45  Polycythemia vera
D47.21  Post-transplant lymphoproliferative disorder (PTLD)
G03.2  Benign recurrent meningitis [Mollaret]
H53.10  Unspecified subjective visual disturbances
H53.11  Day blindness
H53.19  Other subjective visual disturbances
H53.2  Diplopia
J06.9  Acute upper respiratory infection, unspecified
J12.9  Viral pneumonia, unspecified
J15.212  Pneumonia due to Methicillin resistant Staphylococcus aureus
J16.0  Chlamydial pneumonia
J17  Pneumonia in diseases classified elsewhere
J20.0  Acute bronchitis due to Mycoplasma pneumoniae
J20.3  Acute bronchitis due to coxsackievirus
J20.4  Acute bronchitis due to parainfluenza virus
J20.7  Acute bronchitis due to echovirus
K90.81  Whipple's disease
M02.311  Reiter's disease, right shoulder
M02.312  Reiter's disease, left shoulder
M02.321  Reiter's disease, right elbow
M02.322  Reiter's disease, left elbow
M02.331  Reiter's disease, right wrist
M02.332  Reiter's disease, left wrist
M02.341  Reiter's disease, right hand
M02.342  Reiter's disease, left hand
M02.351  Reiter's disease, right hip
M02.352  Reiter's disease, left hip
M02.361  Reiter's disease, right knee
M02.362  Reiter's disease, left knee
M02.371  Reiter's disease, right ankle and foot
M02.372  Reiter's disease, left ankle and foot
M02.38   Reiter's disease, vertebrae
M02.39   Reiter's disease, multiple sites
P35.1   Congenital cytomegalovirus infection
P35.2   Congenital herpesviral [herpes simplex] infection
P35.3   Congenital viral hepatitis
P35.8   Other congenital viral diseases
P35.9   Congenital viral disease, unspecified
P37.0   Congenital tuberculosis
P37.1   Congenital toxoplasmosis
P37.2   Neonatal (disseminated) listeriosis
P37.3   Congenital falciparum malaria
P37.4   Other congenital malaria
P37.8   Other specified congenital infectious and parasitic diseases
P37.9   Congenital infectious or parasitic disease, unspecified
R05     Cough
R11.0   Nausea
R11.10  Vomiting, unspecified
R11.11  Vomiting without nausea
R11.15  Cyclical vomiting syndrome unrelated to migraine
R11.2   Nausea and vomiting, unspecified
R19.7   Diarrhea, unspecified
R21     Rash and other nonspecific skin eruption
R40.0   Somnolence
R40.1   Stupor
R41.0   Disorientation, unspecified
R41.82  Altered mental status, unspecified
R41.89  Other symptoms and signs involving cognitive functions and awareness
R50.9   Fever, unspecified
R51     Headache
R56.00  Simple febrile convulsions
R56.01  Complex febrile convulsions
R56.9   Unspecified convulsions
R75     Inconclusive laboratory evidence of human immunodeficiency virus [HIV]
R87.610 Atypical squamous cells of undetermined significance on cytologic smear of cervix (ASC-US)
R87.611 Atypical squamous cells cannot exclude high grade squamous intraepithelial lesion on cytologic smear of cervix (ASC-H)
R87.612 Low grade squamous intraepithelial lesion on cytologic smear of cervix (LGSIL)
R87.613 High grade squamous intraepithelial lesion on cytologic smear of cervix (HGSIL)
R87.619 Unspecified abnormal cytological findings in specimens from cervix uteri
R87.810 Cervical high risk human papillomavirus (HPV) DNA test positive
Z01.42  Encounter for cervical smear to confirm findings of recent normal smear following initial abnormal smear
Z11.1   Encounter for screening for respiratory tuberculosis
Z11.7   Encounter for testing for latent tuberculosis infection
Z11.3   Encounter for screening for infections with a predominantly sexual mode of transmission
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>Z11.59</td>
<td>Encounter for screening for other viral diseases</td>
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<tr>
<td>Z11.8</td>
<td>Encounter for screening for other infectious and parasitic diseases</td>
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<tr>
<td>Z20.89</td>
<td>Contact with and (suspected) exposure to other communicable diseases</td>
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<td>Z21</td>
<td>Asymptomatic human immunodeficiency virus [HIV] infection status</td>
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<td>Z22.4</td>
<td>Carrier of infections with a predominantly sexual mode of transmission</td>
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<td>Z22.51</td>
<td>Carrier of viral hepatitis B</td>
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<tr>
<td>Z22.52</td>
<td>Carrier of viral hepatitis C</td>
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<td>Z36.85</td>
<td>Encounter for antenatal screening for Streptococcus B</td>
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<td>Z48.22</td>
<td>Encounter for aftercare following kidney transplant</td>
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<td>Z72.51</td>
<td>High risk heterosexual behavior</td>
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<td>Z72.52</td>
<td>High risk homosexual behavior</td>
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<td>Z72.53</td>
<td>High risk bisexual behavior</td>
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<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
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<td>Z94.84</td>
<td>Stem cells transplant status</td>
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### REVISIONS

**01-15-2013**  
In Policy section:  
- Added to the Microorganism chart in item I:  
  "Respiratory Virus Panel - See item IV on page 9 of this policy."
- Added to the medically necessary indication list in item II  
F. Bordetella pertussis  
Code Updates in Policy section:  
- Added CPT codes 87631, 87632, 87633 to item IV (effective 01-01-2013)  
- Corrected coding errors in the Microorganism chart in item I by replacing 87497 with 87797, 87498 with 87798, and 87499 with 87799 as appropriate for the following Microorganisms: Clostridium difficile; Enterovirus; Staphylococcus aureus; Staphylococcus aureus, methicillin resistant; Streptococcus group B; and Trichomonas vaginalis  
- Corrected coding errors in the Note below the Microorganisms chart from, "Note: If NOC codes 87497, 87498, 87499 are billed for PCR for microorganisms when specific codes exist, the claim will be returned for correct coding." To, "Note: If NOC codes 87797, 87798, 87799 are billed for PCR for microorganisms when specific codes exist, the claim will be returned for correct coding."

**11-12-2013**  
Description section updated  
In Policy section:  
- On Item I Trichomonas vaginalis, updated Amplified Probe code from 87798 to 87661 to be used effective 01-01-2014.  
- Changed Trichomonas vaginalis from investigational to medically necessary on the effective date of the policy update.  
In Policy Guidelines:  
- Added to item 2, "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."
- Added item 3, "Many probes have been combined into panels of tests. For the purposes of this policy, other than the respiratory virus panel, only individual probes are reviewed."
- Removed reference to the Association of Molecular Pathology (AMP) website as this is addressed in the Description section.  
Rationale section updated  
In Coding section:  
- Added CPT codes and nomenclatures for CPT codes reflected in the Policy section.  
- ICD-10 codes added.  
References updated.
### Microorganisms

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartonella henselae or quintana</td>
<td>87470 (inv)</td>
<td>87471 (inv)</td>
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<td>Borrelia burgdorferi</td>
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<td>87476 (inv)</td>
<td>87477 (inv)</td>
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<td>Candida species</td>
<td>87480 (med nec)</td>
<td>87481 (inv)</td>
<td>87482 (inv)</td>
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<td>Chlamydia pneumoniae</td>
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<tr>
<td>Chlamydia trachomatis</td>
<td>87490 (med nec)</td>
<td>87491 (med nec)</td>
<td>87492 (inv)</td>
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<td>Clostridium difficile</td>
<td>87493 (med nec)</td>
<td>87798 (inv)</td>
<td>87799 (inv)</td>
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<td>Cytomegalovirus</td>
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<td>87496 (med nec)</td>
<td>87497 (med nec)</td>
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<td>Enterovirus</td>
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<td>87498 (inv)</td>
<td>87799 (inv)</td>
<td></td>
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<tr>
<td>Enterococcus, Vancomycin resistant (e.g., enterococcus vanA, vanB)</td>
<td>87797 (inv)</td>
<td>87500 (med nec)</td>
<td>87799 (inv)</td>
<td></td>
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<td>Gardnerella vaginalis</td>
<td>87510 (med nec)</td>
<td>87511 (inv)</td>
<td>87512 (inv)</td>
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<td>Gastrointestinal Pathogen Panel</td>
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<td>87505 (inv)</td>
<td>87506 (inv)</td>
<td>N/A</td>
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<td></td>
<td></td>
<td>87507 (inv)</td>
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<td>Hepatitis B</td>
<td>87515 (med nec)</td>
<td>87516 (med nec)</td>
<td>87517 (med nec)</td>
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<tr>
<td>Hepatitis C</td>
<td>87520 (med nec)</td>
<td>87521 (med nec)</td>
<td>87522 (med nec)</td>
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<tr>
<td>Hepatitis G</td>
<td>87525 (inv)</td>
<td>87526 (inv)</td>
<td>87527 (inv)</td>
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<tr>
<td>Herpes simplex virus</td>
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<td>87529 (med nec)</td>
<td>87530 (inv)</td>
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<td>Herpes virus-6</td>
<td>87531 (inv)</td>
<td>87532 (inv)</td>
<td>87533 (inv)</td>
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<tr>
<td>HIV-1</td>
<td>87534 (med nec)</td>
<td>87535 (med nec)</td>
<td>87536 (med nec)</td>
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<td>HIV-2</td>
<td>87537 (med nec)</td>
<td>87538 (med nec)</td>
<td>87539 (med nec)</td>
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<td>Influenza virus</td>
<td>See medical policy titled: Influenza Virus Diagnostic Testing and Treatment in the Outpatient Setting</td>
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<td>Legionella pneumophila</td>
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<td>87541 (inv)</td>
<td>87542 (inv)</td>
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</tbody>
</table>

Note: A discussion of every infectious agent that might be detected with a probe technique is beyond the scope of this policy.

I. The status of nucleic acid identification using direct probe, amplified probe, or quantification for the 30 microorganisms listed in the CPT book are summarized in the following table. **NOTE:** "(med nec)" in the chart below applies only when the service is clinically indicated.

**Revised to the current policy from the following prior policy:**

Policy posted 01-16-2015

In Coding section:
- Added CPT Codes: 87505, 87506, 87507, 87623, 87624, 87625 (Effective January 1, 2015)
- Deleted CPT Codes: 87620, 87621, 87622 (Effective January 1, 2015)
<table>
<thead>
<tr>
<th>Microorganism</th>
<th>CPT Codes</th>
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<td>Mycobacterium species</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td>87555 (med nec)</td>
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<tr>
<td>Mycobacterium avium intracellulare</td>
<td>87560 (med nec)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>87580 (inv)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>87590 (med nec)</td>
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<tr>
<td>Papillomavirus</td>
<td>N/A</td>
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</table>

Respiratory Virus Panel

<table>
<thead>
<tr>
<th>Virus</th>
<th>CPT Codes</th>
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</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>87797 (inv)</td>
</tr>
<tr>
<td>Staphylococcus aureus, methicillin resistant</td>
<td>87797 (inv)</td>
</tr>
<tr>
<td>Streptococcus group A*</td>
<td>87650 (med nec)</td>
</tr>
<tr>
<td>Streptococcus group B</td>
<td>87797 (inv)</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>87660 (med nec)</td>
</tr>
</tbody>
</table>

*The direct DNA probe test for streptococcus A is designed to be an alternative to a confirmatory culture. Therefore, the simultaneous use of confirmatory culture and DNA probe test is considered not medically necessary. Antibiotic sensitivity of streptococcus A cultures is frequently not performed for throat cultures. However, if an antibiotic sensitivity is considered, then the most efficient method of diagnosis would be a combined culture and antibiotic sensitivity.

Note: If NOC codes 87797, 87798, 87799 are billed for PCR for microorganisms when specific codes exist, the claim will be returned for correct coding.

II. Other polymerase chain reaction (PCR) testing (87797, 87798, and 87799 describing the use of direct probe, amplified probe, and quantification respectively) for infectious agents that do not have specific CPT codes may be considered medically necessary for the following indications (not an all-inclusive list):

A. Adenovirus - to diagnose adenovirus myocarditis, and infection in immunocompromised hosts, including transplant recipients

B. Avian influenza A virus (H5N1) - with both symptoms consistent with Avian influenza A virus and a history of travel to or contact with persons or birds from a country with documented H5N1 avian influenza infections within 10 days of symptom onset. ([http://www.oie.int/eng/en_index.htm](http://www.oie.int/eng/en_index.htm))

C. Babesiosis (*Babesia*) - when the morphologic characteristics observed on microscopic examination of blood smears do not allow differentiation between Babesia and Plasmodium

D. Bacillus anthracis

E. BK polyomavirus - in transplant recipients and persons with immunosuppressive diseases (e.g., AIDS)

F. Bordetella pertussis

G. *Brucella spp.* - signs and symptoms of Brucellosis

H. *Burkholderia* infections

I. Chancroid (*Haemophilus ducreyi*) - for genital ulcer disease

J. Colorado tick fever virus

K. *Coxiella burnetii* - for acute Q fever

L. Ehrlichiosis (*Ehrlichia*)

M. Epidemic typhus (*Rickettsia prowazekii*)

N. Epstein Barr Virus (EBV) - for detection of EBV in post-transplant lymphoproliferative disorder or for tissue samples with lymphoma and other immunocompromised states

O. *Francisella tularensis*, for diagnosis of tularemia

P. Hemorrhagic fevers of the family *Bunyaviridae* (Rift Valley fever, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndromes) - clinical presentation suggestive of these conditions
Q. Human granulocytic anaplasmosis (formerly *Ehrlichia phagocytophila*)
R. Human metapneumovirus
S. JC polyomavirus - in transplant recipients, immunosuppressive diseases and for progressive multifocal leukoencephalopathy when receiving natalizumab (Tysabri)
T. Leishmaniasis
U. Lymphogranuloma venereum (*Chlamydia trachomatis*)
V. Malaria
W. Measles virus
X. Microsporidia
Y. Mumps
Z. *Neisseria meningitides*
AA. Parvovirus
BB. Psittacosis (*Chlamydia psittaci*)
CC. Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
DD. Severe acute respiratory syndrome (SARS) (coronavirus)
EE. Syphilis (*Treponema pallidum*)
FF. *Toxoplasma gondii*
GG. Varicella-Zoster
HH. West Nile Virus - in tissue specimens
II. Whipple's disease (*T. whippeli*)
JJ. Yersinia pestis

III. The following other quantitative PCR tests (87799) are considered medically necessary:
A. Adenovirus viral load, to monitor response to antiviral therapy in infected immunocompromised hosts, including transplant recipients
B. BK polyomavirus viral load, for diagnosis and monitoring response to therapy in infected kidney transplant recipients
C. Cytomegalovirus (CMV) viral load, to monitor response to therapy
D. Epstein Barr viral load, to monitor for EBV viral replication in solid organ transplant recipients

IV. The Respiratory Virus Panel (87631, 87632, 87633) will be reviewed for medical necessity on a case-by-case basis.

V. PCR testing for the following indications is considered experimental / investigational because of insufficient evidence in the peer-reviewed literature:
A. Actinomycosis
B. Astrovirus
C. Bacterial vaginosis (*Atopobium vaginae, Mobiluncus mulieris, M. curtisi*, *Megasphaera, Bacterial vaginosis Associated Bacteria panel [BVAB]*)
D. Bacteroides spp. (*B. fragilis, B. ureolyticus*)
E. Caliciviruses (noroviruses and sapoviruses)
F. Campylobacteriosis (*Campylobacter infection*)
G. Coccidioidomycosis (*Coccidioides species*)
H. Cryptococcus (*Cryptococcus neoformans*)
I. Cyclosporiasis (*Cyclospora infection*)
J. Dengue fever
K. Donovonosis, or granuloma inguinale (*Klebsiella granulomatis*)
L. Eastern equine encephalitis
M. *Entamoeba histolytica*
N. Genital mycoplasma infections from *Ureaplasma urealyticum* and *Mycoplasma hominis* (unless culture is unavailable)
O. Haemophilus influenzae
P. Hantavirus
Q. Hepatitis A virus
R. Hepatitis D virus
S. Human bocavirus
T. Human herpesvirus type 7 (HHV-7)
U. Human herpesvirus type 8 (HHV-8)
V. Human metapneumovirus
W. LaCrosse encephalitis
X. Leptospirosis (*Leptospira* organisms)
## REVISIONS

<table>
<thead>
<tr>
<th>REVISIONS</th>
<th>03-20-2017 (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y. Molluscum contagiosum</td>
<td></td>
</tr>
<tr>
<td>Z. Moraxella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>AA. Mycoplasma fermentans</td>
<td></td>
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<tr>
<td>BB. Mycoplasma genitalium</td>
<td></td>
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<tr>
<td>CC. Mycoplasma penetrans</td>
<td></td>
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<tr>
<td>DD. Nanobacteria</td>
<td></td>
</tr>
<tr>
<td>EE. Non-albicans Candida</td>
<td></td>
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<tr>
<td>FF. Onychomycosis</td>
<td></td>
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<tr>
<td>GG. Parainfluenza virus</td>
<td></td>
</tr>
<tr>
<td>HH. Peptic ulcer disease (<em>Helicobacter pylori</em>) (other than in persons with MALT lymphomas and marginal zone lymphomas)</td>
<td></td>
</tr>
<tr>
<td>II. Pneumococcal infections (<em>S. pneumoniae</em>)</td>
<td></td>
</tr>
<tr>
<td>JJ. Pneumocystis pneumonia (<em>Pneumocystis jiroveci</em> (formerly <em>P. carinii</em>))</td>
<td></td>
</tr>
<tr>
<td>KK. Prevotella spp.</td>
<td></td>
</tr>
<tr>
<td>LL. Proteus mirabilis</td>
<td></td>
</tr>
<tr>
<td>MM. Pseudomonas (<em>P. aeruginosa</em>)</td>
<td></td>
</tr>
<tr>
<td>NN. Respiratory syncytial virus (RSV)</td>
<td></td>
</tr>
<tr>
<td>OO. Rhinovirus</td>
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<tr>
<td>PP. Rotavirus</td>
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<tr>
<td>QQ. <em>Saccharomyces cerevisiae</em></td>
<td></td>
</tr>
<tr>
<td>RR. Serratia spp. (including <em>S. marcescens</em>)</td>
<td></td>
</tr>
<tr>
<td>SS. Shiga toxin (from <em>E. coli</em> and <em>Shigella</em>)</td>
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</tr>
<tr>
<td>TT. Sporotrichosis (<em>Sporothrix schenckii</em>)</td>
<td></td>
</tr>
<tr>
<td>UU. St. Louis encephalitis</td>
<td></td>
</tr>
<tr>
<td>VV. <em>Staphylococcus saprophyticus</em></td>
<td></td>
</tr>
<tr>
<td>WW. Trichosporonosis (<em>Trichosporon spp.</em>)</td>
<td></td>
</tr>
<tr>
<td>XX. Western equine encephalitis</td>
<td></td>
</tr>
</tbody>
</table>

### Policy Guidelines

1. 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.

2. 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.

3. Many probes have been combined into panels of tests. For the purposes of this policy, other than the respiratory virus panel, only individual probes are reviewed.

### Rationale section updated

- Removed revision details for the following dates: 03-01-2012, 06-05-2012, 11-19-2012

### In Coding section:

- Removed CPT codes: 87475, 87476, 87477
- Removed ICD-9 codes: 487.0-488.19
- Removed ICD-10 codes: J09.x1, J09.x2, J09.x9, J10.00, J10.01, J10.08, J10.1, J10.2, J10.81, J10.82, J10.83, J10.89, J11.00, J11.08, J11.1, J11.2, J11.81, J11.82, J11.83, J11.89
- Added CPT code: 87483
- Added ICD-10 code: A48.2, H53.10, H53.11, H53.19, H53.2, R11.0, R11.10, R11.11, R11.2, R19.7, R21, R40.0, R40.1, R41.0, R41.82, R41.89, R50.9, R51, R56.00, R56.01, R56.9

### References updated


- In the Revisions section:
  - The following clarifications were made to the Revisions chart:
    - The "REVISIONS" header was repeated at the top of each page revisions were reflected.
    - The effective date was repeated on subsequent pages as applicable

- The following clarifications were made to the 03-20-2017 Revision notations:
REVISIONS

10-01-2017
In Coding section:
- Added ICD Code: Z36.85
- Removed ICD Code: Z36

07-17-2019
Description section updated
In Policy section:
- In Item A Microorganism Chart - Bartonella henselae or Quintana – Removed Direct Probe code 87470 and added 87797 (termed due to low volume - no specific replacement code defined)
- In Item A Microorganism Chart added Respiratory syncytial virus (RSV) and related codes.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>87797 (med nec)</td>
<td>87634 (med nec)</td>
<td>N/Ax</td>
</tr>
</tbody>
</table>

- In Item B Microorganism Chart - Hepatitis B virus – Removed Direct Probe code 87515 and added 87797 (termed due to low volume – no specific replacement code defined)

Rationale section updated
In Coding section:
- Removed CPT codes: 87470, 87515
- Added CPT Code: 87634
- Added PLA Codes: 0096U, 0097U, 0098U, 0099U, 0100U

References updated
11-26-2019
In Policy section:
- In Item 9 Human papillomavirus – added "0096U" to Amplified Probe to read "87623 (med nec), 87624 (med nec), 87625 (med nec), 0096U (med nec)"
- In Item E Added "0098U, 0099U, 0100U 0115U" to read "The Respiratory Virus Panel (CPT codes 87631, 87632, 87633, 0098U, 0099U, 0100U, 0115U) will be reviewed for medical necessity on a case-by-case basis."
- In Item F added "0097U" to read "The Gastrointestinal Pathogen Panel (CPT codes 87505, 87506, 87507, 0097U) may be considered medically necessary in patients with:...."

In Coding section:
- Added PLA Code: 0115U (effective 10-01-2019)
- Added ICD-10 Codes: R11.15, Z11.7 (effective 10-01-2019)

REFERENCES

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Other References
1. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee (Gastrointestinal Pathogen Panel, Respiratory Virus Panel, and Meningitis/Encephalitis Panel) - May 2017, July 2018.
2. Blue Cross and Blue Shield of Kansas Pathology Liaison Committee (Gastrointestinal Pathogen Panel, Respiratory Virus Panel, and Meningitis/Encephalitis Panel) - January 2017, May 2018.
3. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee (Gastrointestinal Pathogen Panel, Respiratory Virus Panel, and Meningitis/Encephalitis Panel) - June 2017, August 2018.