FEP 2.04.10 Identification of Microorganisms Using Nucleic Acid Probes

Effective Date: April 1, 2019

Description
Nucleic acid probes are available for the identification of a wide variety of microorganisms. Nucleic acid probes can also be used to quantify 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.

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

- Bartonella henselae or quintana
- Candida species
- Chlamydia trachomatis
- Clostridium difficile
- Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
- Enterovirus
- Gardnerella vaginalis
- Herpes simplex virus
- Human papillomavirus
- Legionella pneumophila

Related Policies:
- 5.01.15 IV Antibiotics Lyme Disease
- 2.04.127 Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis
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- *Mycobacterium* species
- *Mycobacterium tuberculosis*
- *Mycobacterium avium-intracellulare*
- *Mycoplasma pneumoniae*
- *Neisseria gonorrhoeae*
- Respiratory virus panel
- *Staphylococcus aureus*
- *Staphylococcus aureus*, methicillin-resistant
- *Streptococcus*, group A
- *Streptococcus*, group B
- *Trichomonas vaginalis*

The use of nucleic acid testing using a direct or amplified probe technique (*with or without* quantification of viral load) may be considered **medically necessary** for the following microorganisms:

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

The use of nucleic acid testing with quantification of viral load is considered **investigational** for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered medically necessary.

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

- *Chlamydia pneumoniae*
- Hepatitis G virus
- Gastrointestinal pathogen panel
- Central nervous system pathogen panel

**POLICY GUIDELINES**

The use of molecular diagnostics for the diagnosis and management of *Borrelia burgdorferi* infection (Lyme disease) is addressed in evidence review 5.01.15.

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

For uncomplicated infections, testing for only 1 candida species, Candida albicans, may be considered medically necessary. For complicated infections, testing for multiple candida subspecies may be considered medically necessary. The Centers for Disease Control and Prevention (2015) classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or in non-immunocompromised 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.

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.

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

Table PG1. CPT Codes Available for Nucleic Acid Probes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Direct Probe</th>
<th>Amplified Probe</th>
<th>Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartonella henselae or quintana</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enterococcus, vancomycin-resistant (eg, enterococcus vanA, vanB)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal pathogen panel</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system pathogen panel</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis B virus</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis G virus</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Herpes simplex virus</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Herpes virus-6</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV-1</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV-2</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Influenza virus</td>
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<td></td>
<td></td>
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<tr>
<td>Legionella pneumophilia</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mycobacteria species</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mycobacterium avium-intracellulare</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>
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<th>Quantification</th>
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<tr>
<td>Mycoplasma pneumoniae</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Respiratory virus panel</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Staphylococcus aureus, methicillin-resistant</td>
<td></td>
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</tr>
<tr>
<td>Streptococcus, group A</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Streptococcus, group B</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

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

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

<table>
<thead>
<tr>
<th>FDA-Approved/Cleared Diagnostic Test</th>
<th>Test Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus anthracis</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td>Coxiella burnetii (Q fever)</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>PNA FISH</td>
</tr>
<tr>
<td>Escherichia coli and Pseudomonas aeruginosa</td>
<td>PNA FISH</td>
</tr>
<tr>
<td>Escherichia coli and/or Klebsiella pneumoniae and Pseudomonas aeruginosa</td>
<td>PNA FISH</td>
</tr>
<tr>
<td>Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa</td>
<td>PNA FISH</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td>Leishmania</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Real-time PCR</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Multiplex real-time RT-PCR</td>
</tr>
<tr>
<td>Avian flu</td>
<td>Real-time RT-PCR</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>Multiplex real-time RT-PCR</td>
</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>
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FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; PCR: polymerase chain reaction; PNA: peptide nucleic acid; RT: reverse transcriptase.

RATIONALE

Summary of Evidence
For individuals who have suspected *Chlamyphila 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).
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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012</td>
<td>New Policy</td>
<td>Policy updated with literature search, references updated, new information added to rationale for numerous probes. New medically necessary indication added for respiratory virus panel amplified probes.</td>
</tr>
<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review. Added gastrointestinal pathogen panel as investigational to the policy statement. References 1, 27-28, 44-45 and 63-64 added.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 16, 2017; references updated/added. Medically necessary statement added for nonquantified nucleic acid-based testing for enterovirus, Legionella pneumophilia, Mycoplasma pneumoniae, and Bartonella spp, and for quantified testing for human herpesvirus 6. Borrelia testing removed from policy. Investigational policy statement added for probes with quantification of viral load that do not meet criteria for quantification. Investigational statement added for central nervous system pathogen panel.</td>
</tr>
<tr>
<td>March 2019</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 18, 2018; several references updated. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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