Identification of Microorganisms using Nucleic Acid Probes

Policy Number: AHS – M2097 – Identification of Microorganisms Using Nucleic Acid Probes	Prior Policy Name and Number, as applicable:
Effective Date: 01/01/2023	

I. Policy Description

Nucleic acid hybridization technologies utilize complementary properties of the DNA double-helix structures to anneal together DNA fragments from different sources. These techniques are utilized in polymerase chain reaction (PCR) and fluorescent resonance energy transfer (FRET) techniques to identify microorganisms (Khan, 2014).

II. Related Policies

Policy Number	Policy Title
AHS-G2143	Lyme Disease
AHS-G2149	Pathogen Panel Testing
AHS-G2157	Diagnostic Testing of Common Sexually Transmitted Infections
AHS-G2158	Testing for Mosquito- or Tick-Related Infections
AHS-M2057	Diagnosis of Vaginitis Including Multi-Target PCR Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website https://www.cms.gov/medicare-coverage-database/search.aspx or the manual website.

1) The status of nucleic acid identification using direct probe, amplified probe, or quantification for the microorganism's procedure codes is summarized in Table 1 below. "MCC" in the table below indicates that the test **MEETS COVERAGE CRITERIA**; while "DNMCC" tests indicates that the test **DOES NOT MEET COVERAGE CRITERIA.**

Microorganism	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or *quintana*		87471(MCC)	87472 (DNMCC)
Candida species (For vaginitis, please review AHS-M2057 Diagnosis of Vaginitis Including Multi-Target PCR Testing)	87480 (MCC) for vaginitis 87480 (DNMCC) for all other situations except vaginitis	87481 (DNMCC) for all situations	87482 (DNMCC) for all situations
Chlamydia pneumoniae	87485 (MCC)	87486 (MCC)	87487 (DNMCC)
Clostridium difficile	87493 (MCC)		
Cytomegalovirus	87495 (MCC)	87496 (MCC)	87497 (MCC)
Enterococcus, Vancomycin-resistant (e.g., enterococcus vanA, vanB)		87500 (MCC)	
Enterovirus		87498 (MCC)	
Hepatitis B		87516 (MCC)	87517 (MCC)
Hepatitis G	87525 (DNMCC)	87526 (DNMCC)	87527 (DNMCC)
Herpes virus-6	87531 (MCC)	87532 (DNMCC)	87533 (MCC)
Legionella pneumophila	87540 (MCC)	87541 (MCC)	87542 (DNMCC)
Mycoplasma pneumoniae	87580 (MCC)	87581 (MCC)	87582 (DNMCC)
Mycoplasma genitalium		87563 (MCC)	
Respiratory syncytial virus		87634 (MCC)	
Staphylococcus aureus		87640 (MCC)	
Staphylococcus aureus, methicillin resistant		87641 (MCC)	

2) The technique for quantification includes both amplification and direct probes; therefore, simultaneous coding for both amplification or direct probes **DOES NOT MEET COVERAGE CRITERIA**.

3) PCR testing for the following microorganisms that do not have specific CPT codes **MEETS COVERAGE CRITERIA** (not an all-inclusive list):

   a) Actinomyces, for identification of actinomyces species in tissue specimens

b) Adenovirus, to diagnose adenovirus myocarditis, and to diagnose adenovirus infection in immunocompromised hosts, including transplant recipients

c) *Bacillus Anthracis*

d) BK polyomavirus in transplant recipients receiving immunosuppressive therapies and persons with immunosuppressive diseases

e) *Bordetella pertussis* and *B. parapertussis*, for diagnosis of whooping cough in individuals with coughing

f) *Brucella spp*., for members with signs and symptoms of Brucellosis, and history of direct contact with infected animals and their carcasses or secretions or by ingesting unpasteurized milk or milk products

g) *Burkholderia* infections (including B. cepacia, B. gladioli), diagnosis

h) Chancroid (*Haemophilus ducreyi*), for diagnosis of persons with genital ulcer disease

i) *Coxiella burnetii*, for confirmation of acute Q fever

j) EBOLA

k) Epidemic typhus (*Rickettsia prowazekii*), diagnosis

l) Epstein Barr Virus (EBV): for detection of EBV in post-transplant lymphoproliferative disorder; or for testing for EBV in persons with lymphoma; or for those who are immunocompromised for other reasons.

m) *Francisella tularensis*, for presumptive diagnosis of tularemia

n) Hantavirus, diagnosis

o) Hemorrhagic fevers and related syndromes caused by viruses of the family *Bunyaviridae* (Rift Valley fever, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndromes), for diagnosis in acute phase in persons with clinical presentation suggestive of these conditions

p) Hepatitis D virus, for confirmation of active infection in persons with anti-HDV antibodies

q) Hepatitis E virus, for definitive diagnosis in persons with anti-HEV antibodies

r) Human T Lymphotropic Virus type 1 and type 2 (HTLV-I and HTLV-II), to confirm the presence of HTLV-I and HTLV-II in the cerebrospinal fluid of persons with signs or symptoms of HTLV-I/HTLV-II

s) Human metapneumovirus

t) JC polyomavirus, in transplant recipients receiving immunosuppressive therapies, in persons with immunosuppressive diseases, and for diagnosing progressive multifocal leukoencephalopathy in persons with multiple sclerosis or Crohn's disease receiving natalizumab (Tysabri)

u) Leishmaniasis, diagnosis

v) Measles virus (Morbilliviruses), for diagnosis of measles

w) Mumps

x) *Neisseria meningitidis*, to establish diagnosis where antibiotics have been started before cultures have been obtained

y) Parvovirus, for detecting chronic infection in immunocompromised persons

z) Psittacosis, for diagnosis of *Chlamydophila (Chlamydia) psittaci* infection

aa) Rubella, diagnosis

bb) *Toxoplasma gondii*, for detection of T. gondii infection in immunocompromised persons with signs and symptoms of toxoplasmosis, and for detection of congenital *Toxoplasma gondii* infection (including testing of amniotic fluid for toxoplasma infection)

cc) Varicella-Zoster infections

dd) Whipple's disease (T. whippeli), biopsy tissue from small bowel, abdominal or peripheral lymph nodes, or other organs of persons with signs and symptoms, to establish the diagnosis

ee) *Yersinia Pestis*

Policy Guidelines

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

IV. Table of Terminology

Term	Definition
AMA	American Medical Association
CDC	Centers of Disease Control and Prevention
CIDT	Culture-independent diagnostic test
CMV	Cytomegalovirus
CPT	Current procedural terminology
DFA	Direct fluorescent antibody testing
DNA	Deoxyribonucleic acid
DNMCC	Does not meet coverage criteria
EBV	Epstein Barr virus
EVD	Ebola virus disease
FDA	Food and Drug Administration
FRET	Fluorescent resonance energy transfer
H5N1	Hemagglutinin type 5 and neuraminidase type 1 (Avian Influenza A)
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIV 1	Human immunodeficiency virus type 1
HIV 2	Human immunodeficiency virus type 2
HPV	Human papillomavirus
HSV	Herpes simplex virus
HTLV-I	Human t lymphotropic virus type 1
HTLV-II	Human t lymphotropic virus type 2
IDSA	Infectious Diseases Society of America

ITS	Internal transcribed region
MCC	Meets coverage criteria
MRSA	Methicillin-Resistant Staphylococcus Aureus
NAATs	Nucleic acid amplification tests
NGU	Nongonococcal urethritis
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
qPCR	Quantitative polymerase chain reaction
rDNA	Recombinant deoxyribonucleic acid
RNA	Ribonucleic acid
rRT-PCR	Real-time reverse transcriptase-polymerase chain reaction
RSV	Respiratory syncytial virus infection
RT-PCR	Reverse transcriptase-polymerase chain reaction
SARS	Severe acute respiratory syndrome

V. Scientific Background

Nucleic acid hybridization technologies, including polymerase chain reaction (PCR), ligase- or helicase-dependent amplification, and transcription-mediated amplification, are beneficial tools for pathogen detection in blood culture and other clinical specimens due to high specificity and sensitivity (Khan, 2014). The use of nucleic acid-based methods to detect bacterial pathogens in a clinical laboratory setting offers "increased sensitivity and specificity over traditional microbiological techniques" due to its specificity, sensitivity, reduction in time, and high-throughput capability; however, "contamination potential, lack of standardization or validation for some assays, complex interpretation of results, and increased cost are possible limitations of these tests" (Mothershed & Whitney, 2006).

VI. Guidelines and Recommendations

2018 Infectious Diseases Society of America (IDSA)

Specific guidelines for testing of many organisms listed within the policy coverage criteria is found in the updated 2018 Infectious Diseases Society of America (IDSA) guidelines and recommendations titled, "A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology" (Miller et al., 2018). "This document is organized by body system, although many organisms are capable of causing disease in >1 body system. There may be a redundant mention of some organisms because of their propensity to infect multiple sites. One of the unique features of this document is its ability to assist clinicians who have specific suspicions regarding possible etiologic agents causing a specific type of disease. When the term "clinician" is used throughout the document, it also includes other licensed, advanced practice providers. Another unique feature is that in most chapters, there are targeted recommendations and precautions regarding selecting and collecting specimens for analysis for a disease process. It is very easy to access critical information about a specific body site just by consulting the table of contents. Within each chapter, there is a table describing the specimen needs regarding a variety of etiologic agents that one may suspect as causing the illness. The test methods in the tables are listed in priority order according to the recommendations of the authors and reviewers" (Miller et al., 2018).

Centers of Disease Control and Prevention (CDC)

MRSA

The CDC remarks that nucleic acid amplification tests (NAATs, such as PCR) "can be used for direct detection of mecA, the most common gene mediating oxacillin resistance in staphylococci," but will not detect novel resistance mechanisms or uncommon phenotypes (CDC, 2019b).

Candida Auris (C. auris)

The CDC writes that "Molecular methods based on sequencing the D1-D2 region of the 28s rDNA or the Internal Transcribed Region (ITS) of rDNA also can identify *C. auris*." The CDC further notes that various PCR methods have been developed for identifying *C. auris* (CDC, 2020a).

Chlamydia Pneumoniae (C. pneumoniae)

The CDC writes that RT-PCR is the "preferred" method of detecting an acute *C. pneumoniae* infection. The CDC further notes that a positive culture should be confirmed by a second test, such as PCR (CDC, 2021a).

Ebola

The CDC states that for diagnosis of Ebola, "there must be a combination of symptoms suggestive of EVD AND a possible exposure to EVD within 21 days before the onset of symptoms." The CDC notes that PCR is one of the most common diagnostic methods (CDC, 2019a).

Salmonella

The CDC writes that diagnosis requires detection of the *Salmonella* bacteria, be it through culture or a "culture-independent diagnostic test (CIDT)" (CDC, 2019c).

Giardia

The CDC states that microscopy with direct fluorescent antibody testing (DFA) is considered the test of choice for diagnosing giardiasis, but rapid immunochromatographic cartridge assays, enzyme immunoassay kits, microscopy with trichrome staining, and molecular assays may be alternatively used as well. To obtain more accurate test results, the CDC recommends collecting three stool specimens from patients over the course of a few days. But, only molecular testing (e.g., DNA sequencing) can identify *Giardia* strains (CDC, 2021c).

Non-Polio Enterovirus

The CDC remarks that their laboratories "routinely" perform qualitative testing for enteroviruses, parechoviruses, and uncommon picornaviruses (CDC, 2018).

Respiratory Syncytial Virus (RSV)

The CDC writes that real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) and antigen detection tests are the most commonly used diagnostic tests, and are effective in infants and young children. However, the highly sensitive rRT-PCR is recommended to be used when testing older children and adults with RSV (CDC, 2020c).

Mycoplasma Genitalium

The CDC writes that "Men with recurrent NGU [nongonococcal urethritis] should be tested for *M. genitalium* using an FDA-cleared NAAT. If resistance testing is available, it should be performed and the results used to guide therapy. Women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with PID [pelvic inflammatory disease]. Testing should be accompanied with resistance testing, if available. Screening of asymptomatic M. genitalium infection among women and men or extragenital testing for M. genitalium is not recommended. In clinical practice, if testing is unavailable, M. genitalium should be suspected in cases of persistent or recurrent urethritis or cervicitis and considered for PID" (CDC, 2021d).

Miscellaneous

The CDC does not mention the need to quantify [through PCR] *Bartonella*, *Legionella pneumophila,* or *Mycoplasma pneumoniae.* However, PCR can be performed for both *Legionella pneumophila* and *Mycoplasma pneumonia*e specimen (CDC, 2020b, 2021b, 2022). No guidance was found on Hepatitis G.

Committee on Infectious Diseases, American Academy of Pediatrics, 31st Edition (2018-2021, Red Book)

The Committee on Infectious Diseases released joint guidelines with the American Academy of Pediatrics. In it, they note that "the presumptive diagnosis of mucocutaneous candidiasis or thrush usually can be made clinically." They also state that FISH probes may rapidly detect *Candida* species from positive blood culture samples, although PCR assays have also been developed for this purpose (Pediatrics, 2018).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

As of 04/19/2022, a list of current U.S. Food and Drug Administration (FDA, 2022) approved or cleared nucleic acid-based microbial tests is available at: https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
87471	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, amplified probe technique
87472	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, quantification
87480	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique
87481	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique
87482	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, quantification
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
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
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
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
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
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
87563	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma genitalium, amplified probe technique
87580	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, direct probe technique
87581	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, amplified probe technique
87582	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, quantification
87634	Infectious agent detection by nucleic acid (DNA or RNA); respiratory syncytial virus, amplified probe technique
87640	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, amplified probe technique
87641	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, methicillin resistant, amplified probe technique
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

IX. Evidence-based Scientific References

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X. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
04/12/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria.
09/14/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria. Edits made for clarity:

	Removed "*DNMCC= Does Not Meet Coverage Criteria; MCC = Meets coverage criteria." from beneath the table in CC1, as the definition was redundant with what was already provided in CC1. Revised code disclaimer statement