BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Identification of Microorganisms using Nucleic Acid Probes AHS – M2097

File Name: identification_of_microorganisms_using_nucleic_acid_probes
Origination: 01/2019
Last Review: 07/2023

Description of Procedure or Service

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).

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, only individual probes are reviewed.

For guidance on nucleic acid identification of *Candida* in vaginitis, please refer to AHS-M2057-Diagnosis of Vaginitis Including Multi-Target PCR Testing.

Related Policies
Hepatitis Testing AHS – G2036
Lyme Disease AHS – G2143
Pathogen Panel Testing AHS – G2149
Diagnostic Testing of Common Sexually Transmitted Infections AHS – G2157
Testing for Vector-Borne Infections AHS – G2158
Diagnosis of Vaginitis Including Multi-Target PCR Testing AHS – M2057

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for identification of microorganisms using nucleic probes when it is determined the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Identification of Microorganisms Using Nucleic Acid Probes is covered

1. Reimbursement of nucleic acid identification using direct probe, amplified probe, or quantification is allowed for the microorganism's procedure codes summarized in Table 1 below:

Microorganism	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or Quintana		87471	
Chlamydia pneumoniae	87485	87486	
Clostridium difficile		87493	
Cytomegalovirus	87495	87496	87497
Enterococcus, Vancomycin-resistant (e.g., enterococcus vanA, vanB)		87500	
Enterovirus		87498	
Herpes virus-6	87531		87533
Legionella pneumophila	87540	87541	
Mycoplasma pneumoniae	87580	87581	
Mycoplasma genitalium		87563	
Orthopoxvirus		87593	
Respiratory syncytial virus		87634	
Staphylococcus aureus		87640	
Staphylococcus aureus, methicillin resistant		87641	

When Identification of Microorganisms Using Nucleic Acid Probes is not covered

Reimbursement is not allowed for nucleic acid identification using direct probe, amplified probe, or quantification for the microorganism's procedure codes summarized in Table 1 below:

Microorganism	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or Quintana			87472
Non-vaginal *Candida* species	87480	87481	87482
Chlamydia pneumoniae			87487
Hepatitis G	87525	87526	87527
Herpes virus-6		87532	

Legionella pneumophila			87542
Mycoplasma pneumoniae			87582

Reimbursement is not allowed for simultaneous ordering of any combination of direct probe, amplified probe, and/or quantification for the same organism in a single encounter.

Policy Guidelines

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).

Guidelines and Recommendations

World Health Organization (WHO)

For detection of monkeypox, the WHO recommends "detection of viral DNA by polymerase chain reaction (PCR)" as the preferred laboratory test and recommends that any individual with a suspected case should be offered testing. They note that the best specimens for diagnosis are taken directly from the rash. Antigen and antibody detection may not be able to distinguish between orthopoxviruses (WHO, 2022).

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)

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." Such exposures include

- blood or body fluids from a person sick with or who died from EVD,
- objects contaminated with blood or body fluids of a person sick with or who died from EVD,
- infected fruit bats and nonhuman primates (apes or monkeys), or
- semen from an individual who has recovered from EVD.

The CDC notes that PCR is one of the most common diagnostic methods, but also cautions that "When the virus is no longer present in great enough numbers in a patient's blood, PCR methods will no longer be effective. Other methods, based on the detection of antibodies an EVD case produces to an infection, can then be used to confirm a patient's exposure and infection by Ebola virus" (CDC, 2022c).

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, 2021b).

Monkeypox Virus

The CDC defines a suspect case of monkeypox as a "new characteristic rash, or meets one of the epidemiologic criteria and has a high clinical suspicion for monkeypox." A probable case is defined as "no suspicion of other recent Orthopoxvirus exposure (e.g., Vaccinia virus in ACAM2000 vaccination) AND demonstration of the presence of Orthopoxvirus DNA by polymerase chain reaction of a clinical specimen OR Orthopoxvirus using immunohistochemical or electron microscopy testing methods OR Demonstration of detectable levels of anti-orthopoxvirus IgM antibody during the period of 4 to 56 days after rash onset." A confirmed case of monkeypox is defined as "demonstration of the presence of Monkeypox virus DNA by polymerase chain reaction testing or Next-Generation sequencing of a clinical specimen OR isolation of Monkeypox virus in culture from a clinical specimen" (CDC, 2022b).

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, 2019a).

Mycoplasma genitalium

For individuals with a penis who are experiencing recurrent nongonococcal urethritis (NGU), the CDC recommends FDA-cleared NAAT, with resistance testing done when available. The CDC also recommends that individuals with recurrent cervicitis should be tested for *M. genitalium*. Testing should be considered for individuals with pelvic inflammatory disease (PID). Testing should be accompanied with resistance testing, if available. The CDC does not recommend screening for *M. genitalium* for asymptomatic individuals, nor do they recommend extragenital testing for *M. genitalium*. "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).

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, 2022d).

Salmonella

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

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, 2021c, 2022a). 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 (AAP Committee on Infectious Diseases, 2018)

European Centre for Disease Prevention and Control (ECDC)

On May 23, 2022, the ECDC released a rapid risk assessment of the monkeypox multi-country outbreak. They recommend that patients with probable cases should be tested with a "monkeypox virus specific PCR or an orthopoxvirus specific PCR assay which is then confirmed through sequencing" (ECDC, 2022b).

On June 2, 2022, ECDC released interim advice on risk communication and community engagement during the 2022 monkeypox outbreak in Europe. This is a joint report with the WHO regional office for Europe. They recommend speaking to your doctor about getting tested for monkeypox if you develop a rash with a fever or feeling of discomfort or illness (ECDC, 2022a).

United Kingdom Heath Security Agency (UKHSA)

The UKHSA states that "Mpox is diagnosed by PCR test for the monkeypox virus (MPXV) on a viral swab taken from one or more vesicles or ulcers." Specifically, it is recommended that healthcare workers "Take a viral swab in viral culture medium or viral transport medium (for example Virocult®) from an open sore or from the surface of a vesicle. If other wounds are present, ensure that the sample is definitely taken from a vesicle, an ulcer or a crusted vesicle. Rub the swab over the lesion and place the swab in the collection tube. If there are pharyngeal lesions, a throat swab should also be taken" (UKHSA, 2023). UKHSA also suggests that "A viral throat swab can be taken for high-risk contacts of a confirmed or highly probable case who have developed systemic symptoms but do not have a rash or lesions that can be sampled. Please note that even if the throat swab is negative, the individual must continue with monitoring and isolation as instructed by their local health protection team, and should be reassessed and sampled if further symptoms develop". Lastly, "If follow-up testing is required from a confirmed or highly probable case, either because of clinical deterioration or to inform discharge from isolation to an inpatient setting, additional samples should be taken and should include the following:

- a lesion swab and throat swab in viral transport medium
- a blood sample in an EDTA tube
- a urine sample in a universal sterile container" (UKHSA, 2023).

State and Federal Regulations, as applicable

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.

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 87471, 87472, 87480, 87481, 87482, 87485, 87486, 87487, 87493, 87495, 87496, 87497, 87498, 87500, 87525, 87526, 87527, 87531, 87532, 87533, 87540, 87541, 87542, 87563, 87580, 87581, 87582, 87593, 87634, 87640, 87641.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

AAP Committee on Infectious Diseases. (2018). *Red Book® 2018*.

CDC. (2018, November 14). Non-Polio Enterovirus, CDC Laboratory Testing & Procedures. Retrieved from https://www.cdc.gov/non-polio-enterovirus/lab-testing/testing-procedures.html

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CDC. (2020a, May 29). Identification of Candida auris. Retrieved from https://www.cdc.gov/fungal/candida-auris/identification.html

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ECDC. (2022a). *Interim advice on Risk Communication and Community Engagement during the monkeypox outbreak in Europe, 2022*. Retrieved from https://www.ecdc.europa.eu/sites/default/files/documents/Joint-ECDC-WHO-interim-advice-on-RCCE-for-Monkeypox-2-June-2022.pdf

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Khan, A. (2014). Rapid Advances in Nucleic Acid Technologies for Detection and Diagnostics of Pathogens. *J Microbiol Exp, 1*(2). doi:10.15406/jmen.2014.01.00009

Miller, J. M., Binnicker, M. J., Campbell, S., Carroll, K. C., Chapin, K. C., Gilligan, P. H., . . . Yao, J. D. (2018). 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. *Clinical Infectious Diseases*, ciy381-ciy381. doi:10.1093/cid/ciy381

Mothershed, E. A., & Whitney, A. M. (2006). Nucleic acid-based methods for the detection of bacterial pathogens: present and future considerations for the clinical laboratory. *Clin Chim Acta, 363*(1-2), 206-220. doi:10.1016/j.cccn.2005.05.050

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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

Specialty Matched Consultant Advisory Panel review 3/2021

Medical Director review 3/2021

Medical Director review 7/2022

Medical Director review 11/2022

Medical Director review 7/2023

Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for identification of microorganisms using nucleic probes when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Billing/Coding section updated. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

12/10/19 Reviewed by Avalon 3rd Quarter 2019 CAB. Within the table under the When Covered section, removed “Gastrointestinal Pathogen Panel” and corresponding codes 87505-87507 and “Respiratory Virus Panel” including corresponding codes 87631-87633; Item 3, removed C. dificile and added Mycoplasma genitalium. Under the When Not Covered section, added “Candida species” along w/corresponding codes. The following codes were removed from the Billing/Coding section: 87505, 87506, 87507, 87632, 87633. Medical Director review 11/2019. (jd)

5/12/20 Updated Related Policies section. Under the When Covered section, added item #3: "Reimbursement is allowed for molecular testing for coronavirus disease 2019 (COVID-19) to aid diagnosis." Updated Policy guidelines and references. Added the following codes to the Billing/Coding section: U0001, U0002, and 87635. Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 4/2020. (jd)

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Added Note to Policy statement as follows: "The coverage criteria outlined in this policy are not applicable to diagnostic COVID-19 testing." To Table 1 When Covered section table 1, added the following: Chlamydia pneumoniae, Mycoplasma genitalium, Respiratory syncytial and associated codes; removed HIV 1 and 2. Removed the following statements: "Reimbursement is allowed for PCR testing for Ebola…" and will currently be submitted with unspecified codes along with statement related to coronavirus disease 2019. Item 2: removed statement related to Avian influenza A virus, mycoplasma genitalium, statements related to RSV and SARS, and added "EBOLA". Policy and references updated. The following codes were removed from the tables and Billing/Coding section: U0001, U0002 and 87635, 87534, 87535, 87536, 87537, 87538 and 87539. Medical Director review 7/2020. (jd)

10/1/20 The following code was added to the Billing/Coding section effective 10/1/20: 0219U. (jd)

3/31/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)

8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Policy guidelines and references updated. Medical Director review 7/2021. (jd)

9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB. Updated background, policy guidelines and references. Policy and When Covered section edited for clarity. Billing/coding section updated. Medical Director review. 7/2022. (tm)

12/13/22 Off-cycle review by Avalon 3rd Quarter 2022 CAB. Policy Guidelines and References updated. Table 1 in When Covered section updated to include Orthopoxvirus and code 87593 added to Amplified Probe column. Coverage criteria 2 edited to remove specific list of organisms, as it was not all inclusive. Now reads "2. Reimbursement is allowed for PCR testing for any other microorganism without a specific CPT code." When Not Covered section edited for clarity. Code 87593 added to Billing/Coding section. Medical Director review 11/2022. (tm)

8/15/23 Reviewed by Avalon 2nd Quarter 2023 CAB. Updated Description, Policy Guidelines and References. Within the table under the When Covered section, row for Candida testing for vaginitis removed (see updates to Table 1 under Not Covered), directive to see M2057 for vaginal Candida moved into policy description, code 87493 for C. diff moved from "Direct Probe" column to "Amplified Probe" column, Hepatitis B removed from the table due to the expansion of G2036 to include Hepatitis B testing. Previous coverage criteria 2 removed (2. "Reimbursement is allowed for PCR testing for any other microorganism without a specific CPT code"). Table 1 under Not Covered section edited to remove references to Candida testing for vaginitis, row now specifies "non-vaginal Candida". Removed codes 87516, 87517, 87797, 87798, and 87799 from Billing/Coding section. Medical Director review 7/2023. (tm)