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Medical Policy Manual Genetic Testing, Policy No. 85

Identification of Microorganisms Using Nucleic Acid Probes

Effective: October 1, 2022

Next Review: July 2023
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Nucleic acid probes are available for the identification of a wide variety of microorganisms and 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.

MEDICAL POLICY CRITERIA

Note: Nucleic acid testing for the SARS-CoV-2 virus (COVID-19) is addressed in a separate policy (see Cross References).

I. The use of nucleic acid testing using a direct or amplified probe technique (with or without quantification) may be considered **medically necessary** for one or more of the following microorganisms:
   A. Cytomegalovirus
   B. Hepatitis B virus
   C. Hepatitis C virus
   D. HIV-1

E. HIV-2

F. Human herpesvirus 6

G. Influenza virus

II. The use of nucleic acid testing is considered **investigational** for the following (see Policy Guidelines):

A. Testing with quantification or semi-quantification for microorganisms that *are not* included in the list of microorganisms for which probes with or without quantification are considered medically necessary (see Criterion I above).

B. Central nervous system pathogen panels and nucleic acid testing for the Hepatitis G virus.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Table 1. CPT Codes for Nucleic Acid Probes

Pathogen	Direct Probe	Amplified Probe	Quantification
Bartonella henselae or *quintana*		87471	87472 [investigational]
Candida species	87480	87481	87482 [investigational]
Chlamydophila pneumoniae	87485	87486	87487 [investigational]
Chlamydia trachomatis	87490	87491	87492 [investigational]
Cytomegalovirus	87495	87496	87497
Gardnerella vaginalis	87510	87511	87512 [investigational]
Hepatitis B virus		87516	87517
Hepatitis C virus	87520	87521	87522
Hepatitis G virus	87525 [investigational]	87526 [investigational]	87527 [investigational]
Herpes simplex virus	87528	87529	87530 [investigational]
Herpes virus-6	87531	87532	87533
HIV-1	87534	87535	87536
HIV-2	87537	87538	87539
Human papillomavirus		87623-87625	
Influenza virus		87501-87503	
Legionella pneumophila	87540	87541	87542 [investigational]
Mycobacteria species	87550	87551	87552 [investigational]
Mycobacterium tuberculosis	87555	87556	87557 [investigational]
Mycobacterium avium-intracellulare	87560	87561	87562 [investigational]
Mycoplasma pneumoniae	87580	87581	87582 [investigational]
Neisseria gonorrhoeae	87590	87591	87592 [investigational]
Streptococcus, group A	87650	87651	87652 [investigational]
Panels			
Semi-quantitative respiratory panel	0151U [investigational]		

Panels	
Central nervous system pathogen panel	87483 [investigational]

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.

CROSS REFERENCES

1. COVID-19 Testing, Laboratory, Policy No. 74

BACKGROUND

NUCLEIC ACID PROBES

A nucleic acid probe is used to detect and identify species or subspecies of organisms by identifying nucleic acid sequences in a sample. Nucleic acid probes detect genetic materials, such as RNA or DNA, unlike other tests, which use antigens or antibodies to diagnose organisms.

The availability of nucleic acid probes has permitted the rapid direct identification of microorganism DNA or RNA. Amplification techniques result in exponential increases in copy numbers of a targeted strand of microorganism-specific DNA. The most 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).

The direct probe technique, amplified probe technique, and probe with quantification methods vary based on 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.

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.

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 (e.g., HIV), fastidious or lengthy culture requirements (e.g., *Mycobacteria*, *Chlamydia*, *Neisseria* species), or difficulty in collecting an appropriate sample (e.g., 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.

The risks of nucleic acid testing include false-positive and false-negative results; inaccurate identification of pathogens by the device, inaccurate interpretation of test results, or incorrect operation of the instrument.

- False-positive results can lead to unnecessary treatment, with its associated toxicities and side effects, including allergic reaction. In addition, true diagnosis and treatment could be delayed or missed altogether.
- False-negative results could delay diagnosis and initiation of proper treatment.

- It is possible that these risks can be mitigated by the use of a panel of selected pathogens indicated by the clinical differential diagnosis while definitive culture results are pending.

REGULATORY STATUS

A list of current U.S. Food and Drug Administration-approved or cleared nucleic acid-based microbial tests is available online.[1]

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

This evidence review focuses on the clinical validity and clinical utility.

CENTRAL NERVOUS SYSTEM BACTERIAL AND VIRAL PANELS

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 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) 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*.

The systematic review and meta-analysis by Tansarli and Chapin (2019) examined the diagnostic accuracy of the BioFire FilmArray ME panel.[2] Thirteen prospective and retrospective studies conducted from 2016 through 2019 were reviewed (n=3,764 patients); eight were included in the meta-analysis (n=3,059 patients). Included in the meta-analysis is the study by Leber [2016],[3] which is discussed below. Risk of bias among the studies was mixed but tended toward low risk, with the index test aspect being most questionable. No applicability concerns were found in any studies. To be eligible, studies had to provide sensitivity and specificity data compared with a reference standard. Patients in the studies had infections caused by a variety of components found on the panel (bacterial, viral, Cryptococcus neoformans/gatti). Table 2 summarizes the sensitivity, specificity, and other measurements of accuracy. The highest proportions of false-positive results were for *Streptococcus pneumoniae* (17.5%) and *Streptococcus agalactiae* (15.4%). The highest proportion of false negatives was seen for Herpes Simplex Virus 1 and 2, *Enterovirus*, and *C. neoformans/gatti*. The rate of false-positive results with the ME panel suggests this method should be used with caution, and additional diagnostic methods should be used to confirm panel results.

Table 2. Accuracy of BioFire FilmArray Meningitis/Encephalitis Panel

Measurement	Sensitivity, mean %	Specificity, mean %	PPV, %	NPV, %	False-Positives Before and After Adjudication[a], %		False-Negatives Before and After Adjudication, %	
					Before	After	Before	After
Value	90.2	97.7	85.1	98.7	11.4	4.0	2.2	1.5
95% CI	86.2-93.1	94.6-99.0	NR	NR	NR	NR	NR	NR
Range	60-100	88-100	NR	NR	NR	NR	NR	NR

Source: Tansarli and Chapin (2019)[2]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

[a] Adjudication is further investigation of results, which could include further testing, clinician input, or chart review. In this study it was performed for discordant results between index and reference tests.

The study by Leber (2016) was the FDA pivotal study, as well as the largest and one of the only prospective studies available.[3] A total of 1,560 samples were tested from children and adults with available CSF, but not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis. (See Table 3 for study characteristics.) 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 were 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 five 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 limitations are shown in Tables 5 and 6.

Table 3. Characteristics of Clinical Validity Studies of CNS Panel

Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Leber (2016)[3]	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	Nonconcurrent prospective	Culture and PCR	Processed within seven days of collection or immediately frozen for future testing	Yes
Hanson (2016)[4]	Children and adults from whom a CSF specimen was available who had been tested with at least one conventional method	Retrospective, selection method not clear	Culture and PCR with discrepancy resolution LDT PCR	Stored up to two years after collection	Yes
Graf (2017)[5]	Positive samples (children) selected based on positivity of reference method for any of targets on the CNS panel. Negative samples selected based on negativity of reference sample and with preference for samples highly suggestive of meningitis or encephalitis	Retrospective, convenience	Culture and PCR	Stored up to two years after collection	NR

CNS: central nervous system; CSF: cerebrospinal fluid; LDT: laboratory-developed test; NR: not reported; PCR: polymerase chain reaction.

Table 4. Results of Clinical Validity Studies of CNS Panel

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/ Positive % Agreement	Specificity/ Negative % Agreement
Leber (2016)[3]	1,643	1,560	Insufficient volume, outside the seven-day window, repeat subject, or invalid FilmArray test.			

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/ Positive % Agreement	Specificity/ Negative % Agreement
Bacteria						
Escherichia coli K1				0.1	100 (34 to 100)	99.9 (99.6 to 100)
Haemophilusinfluenzae				0.06	100 (NA)	99.9 (99.6 to 100)
Listeria monocytogenes				0		100 (99.8 to 100)
Neisseria meningitides				0		100 (99.8 to 100)
Streptococcus agalactiae				0.06	0 (NA)	99.9 (99.6 to 100)
Streptococcus pneumoniae				0.3	100 (51 to 100)	99.2 (98.7 to 99.6)
Viruses						
Cytomegalovirus				0.2	100 (44 to 100)	99.8 (99.4 to 99.9)
Enterovirus				2.9	96 (86 to 99)	99.5 (99.0 to 99.8)
Herpes simplex virus 1				0.1	100 (34 to 100)	99.9 (99.5 to 100)
Herpes simplex virus 2				0.6	100 (72 to 100)	99.9 (99.5 to 100)
Human herpesvirus 6				1.3	86 (65 to 95)	99.7 (99.3 to 99.9)
Human parechovirus				0.6	100 (70 to 100)	99.8 (99.4 to 99.9)
Varicella zostervirus				0.3	100 (51 to 100)	99.8 (99.4 to 99.9)
Yeast						
Cryptococcus neoformans/ Cryptococcus gattii				0.06	100 (NA)	99.7 (99.3 to 99.9)
Hanson et al (2016)[4]	342	342	NR			
Bacteria						
Escherichia coli K1				0.3	100 (3 to 100)	100 (98 to 100)
Haemophilus influenza				1.5	100 (48 to 100)	100 (97 to 100)
Listeria monocytogenes				0	NA	100 (98 to 100)
Neisseria meningitides				0.3	100 (3 to 100)	100 (98 to 100)
Streptococcus agalactiae				0.9	67 (9 to 99)	99 (95 to 100)
Streptococcus pneumoniae				1.5	100 (48 to 100)	99 (96 to 100)

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/ Positive % Agreement	Specificity/ Negative % Agreement
Viruses						
Cytomegalovirus				2.0	57 (18 to 90)	100 (91 to 100)
Enterovirus				11.1	97 (86 to 100)	100 (69 to 100)
Herpes simplex virus 1				3.5	93 (66 to 100)	98 (89 to 100)
Herpes simplex virus 2				8.5	100 (88 to 100)	100 (82 to 100)
Human herpesvirus 6				5.6	95 (74 to 100)	100 (93 to 100)
Human parechovirus				0.3	100 (3 to 100)	100 (93 to 100)
Varicella zostervirus				9.4	100 (89 to 100)	100 (79 to 100)
Yeast						
Cryptococcus neoformans/ Cryptococcus gattii				2.6	64 (35 to 87)	NA
Graf (2017)[5]	133	133	NR			
Bacteria						
Haemophilus influenzae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus agalactiae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus pneumoniae				NA[a]	100 (28 to 100)[b]	100 (96 to 100)[b]
Viruses						
Enterovirus				NA[a]	95 (82 to 99)[b]	100 (94 to 100)[b]
Herpes simplex virus 1				NA[a]	50 (7 to 93)[b]	100 (96 to 100)[b]
Herpes simplex virus 2				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Human herpesvirus 6				NA[a]	100 (9 to 100)[b]	100 (96 to 100)[b]
Human parechovirus				NA[a]	94 (70 to 100)[b]	100 (95 to 100)[b]

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

[a] Positives and negatives retrospectively selected from a convenience sample with different selection criteria; prevalence is unknown.

[b] Confidence intervals not provided in publication; estimated based on available information.

Table 5. Relevance Limitations of Studies of CNS Panel

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Leber (2016)[3]	4. Participants not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis	3. Used investigational version of test but varies from marketed version only in that Epstein-Barr virus is not available in the marketed version			
Hanson (2016)[4]	3. Selection criteria with respect to clinical characteristics not described	3. Used investigational version (see above)			
Graf (2017)[5]	4. Selection criteria varied for positive and negative samples				

FN: false-negative; FP: false-positive; TN: true negative; TP: true positive.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Gaps

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Follow-Up Completeness[e]	Statistical[f]
Leber (2016)[3]			2. Many tests performed on frozen samples			
Hanson (2016)[4]	1. Not clear if participants were consecutive		2. Many tests performed on frozen samples		1. Not clear if there were indeterminate samples	
Graf (2017)[5]	3. Selection not random or consecutive	1. Not clear if blinded	2. Many tests performed		1. Not clear if there were indeterminate samples	1. Confidence intervals not provided

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Follow-Up Completeness[e]	Statistical[f]
	and varied for positive and negatives		on frozen samples			

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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.

PRACTICE GUIDELINE SUMMARY

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

The CDC has published a number of recommendations and statements regarding the use of nucleic acid amplification tests (NAATs) to diagnose viruses and infections.

In 2019, the CDC published guidance for laboratory testing for Cytomegalovirus (CMV), the guideline stated that the standard laboratory test for congenital CMV is PCR on saliva, with confirmation via urine test to avoid false-positive results from ingesting breast milk from CMV seropositive mothers. Serologic tests were recommended for person >12 months of age.[6]

INFECTIOUS DISEASE SOCIETY OF AMERICA (IDSA)

In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis.[7] When making diagnostic recommendations, the IDSA notes cultures as the standard of care in diagnosing healthcare-associated ventriculitis and meningitis, but that “nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (strength of recommendation: weak, quality of evidence: low).”

SUMMARY

There is enough research to show that nucleic acid probe testing with quantification can help improve health outcomes for patients with cytomegalovirus, hepatitis B, hepatitis C, HIV-1, HIV-2, human herpesvirus 6, and influenza virus. In many cases, this testing is considered standard of care for monitoring treatment for affected patients. Therefore, 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 these viruses.

There is not enough research to show that nucleic acid probe testing with quantification or semi-quantification for microorganisms other than cytomegalovirus, hepatitis B, hepatitis C, HIV-1, HIV-2, human herpesvirus 6, and influenza virus can improve health outcomes for patients. Therefore, nucleic acid testing with quantification or semi-quantification is considered investigational when medical necessity criteria are not met.

There is not enough research to show that nucleic acid probe testing for hepatitis G can improve health outcomes in individuals who have hepatitis. In addition to the lack of evidence on the test performance, the clinical implications of these tests are unclear. Also, there are no clinical guidelines based on research that recommend nucleic acid probe testing for hepatitis G. Therefore, this testing, either with or without quantification, is considered investigational.

There is not enough research to show that a nucleic acid-based central nervous system pathogen panel testing can improve health outcomes for individuals who have signs and/or symptoms of meningitis and/or encephalitis. The available central nervous system panel is highly specific for the included organisms, but the sensitivity for each pathogen is not well-characterized. In addition, the false-positive rate for this panel was more than 15%, and a negative test result does not exclude infection due to pathogens not included in the panel. Also, there are no clinical guidelines based on research that recommend nucleic acid-based central nervous system pathogen panel testing. Therefore, this testing is considered investigational.

REFERENCES

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CODES

NOTE: CPT codes for quantification include both amplification and direct probes; therefore, simultaneous coding for both quantification with either amplification or direct probes is not warranted.

Codes	Number	Description
CPT	~~0151U~~	~~Infectious disease (bacterial or viral respiratory tract infection), pathogen specific nucleic acid (DNA or RNA), 33 targets, real-time semi-quantitative PCR, bronchoalveolar lavage, sputum, or endotracheal aspirate, detection of 33 organismal and antibiotic resistance genes with limited semi-quantitative results~~ (Deleted 04/01/2022)
	0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi
	87472	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, quantification
	87482	;Candida species, quantification
	87483	;central nervous system pathogen (eg, Neisseria meningitidis, Streptococcus pneumoniae, Listeria, Haemophilus influenzae, E. coli, Streptococcus agalactiae, enterovirus, human parechovirus, herpes simplex virus type 1 and 2, human herpesvirus 6, cytomegalovirus, varicella zoster virus, Cryptococcus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets
	87487	;Chlamydia pneumoniae, quantification
	87497	;cytomegalovirus, quantification
	87501	;influenza virus, includes reverse transcription, when performed, and amplified probe technique, each type or subtype
	87502	;influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, first 2 types or sub-types
	87503	;influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, each additional influenza virus type or sub-type beyond 2 (List separately in addition to code for primary procedure)
	87512	;Gardnerella vaginalis, quantification

Codes	Number	Description
	87517	;hepatitis B virus, quantification
	87522	;hepatitis C, quantification, includes reverse transcription when performed
	87525	;hepatitis G, direct probe technique
	87526	;hepatitis G, amplified probe technique
	87527	;hepatitis G, quantification
	87530	;Herpes simplex virus, quantification
	87533	;Herpes virus-6, quantification
	87536	;HIV-1, quantification, includes reverse transcription when performed
	87539	;HIV-2, quantification, includes reverse transcription when performed
	87542	;Legionella pneumophila, quantification
	87552	;Mycobacteria species, quantification
	87557	;Mycobacteria tuberculosis, quantification
	87562	;Mycobacteria avium-intracellulare, quantification
	87582	;Mycoplasma pneumoniae, quantification
	87592	;Neisseria gonorrhoeae, quantification
	87652	;Streptococcus, group A, quantification
HCPCS	None	

Date of Origin: *July 2019*