Clinical Policy: Infectious Disease: Multi-System Lab Testing

Reference Number: TX.CP.MP.302
Effective Date: 03/24

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

I. Description

Some pathogens cause infections with symptoms that affect a primary body system, while others cause infections that affect multiple body systems. This policy outlines the appropriate use of tests for pathogens that can cause multisystem symptoms and/or infections. Tests for pathogens that infect multiple body systems can be targeted to detect a specific pathogen(s) or non-targeted to broadly detect nucleic acid from any potential pathogen.

Cytomegalovirus (CMV) is a common infection that does not usually cause problems in healthy individuals. However, it is of particular concern in individuals with weakened immune systems (e.g., organ transplant recipients), and can lead to signs and symptoms such as fever, sore throat, swollen glands, extreme fatigue/malaise, mononucleosis, or hepatitis, and increased risk of poor outcomes (morbidity/mortality). Additionally, infections during pregnancy can lead to infection of the fetus (congenital CMV infection). One in 5 babies with congenital CMV infection will have long term health impacts, such as hearing loss, vision impairment, or small head size (microcephaly).

Metagenomic sequencing, a newer, more generalized technique, can detect multiple organisms' genomes within a single specimen. While these new tests have potential benefits, challenges remain to be explored prior to routine clinical adoption, such as whether they can reliably discern predominantly host genomic material from a small amount of pathogen genomic material or active infection from colonization, among others.

Note: This policy is applicable to laboratory services delivered in an outpatient setting.

II. Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that the specific tests noted below are **medically necessary** when meeting the related criteria:

i. CYTOMEGALOVIRUS TESTS

A. Cytomegalovirus (CMV) antibody tests may be considered medically necessary when:

1. The member is a prospective organ transplant donor or recipient undergoing pre-transplant evaluation or the member has suspected mononucleosis; and

2. The member had negative testing for Epstein-Barr Virus (EBV) or the member is pregnant; and
3. The member has symptoms of active CMV infection, **or h**as ultrasound findings consistent with in utero CMV infection.
4. Current evidence does not support the use of cytomegalovirus (CMV) antibody tests for all other indications.

B. Cytomegalovirus (CMV) nucleic acid/PCR or antigen detection tests may be considered medically necessary when:

1. The member is immune-compromised or the member is 12 months of age or younger; and;
2. The member is a prospective organ transplant donor or recipient undergoing pre-transplant evaluation, is undergoing post-transplant monitoring, is a newborn with very low birth weight (less than 1500 grams or 3 lbs 4.9 oz), is a premature newborn (born before 37 weeks 0 days gestation), an infant with suspected congenital CMV infection (signs/symptoms of congenital CMV infection such as congenital hearing loss, documented maternal CMV infection, or ultrasound findings consistent with in utero CMV infection), or is pregnant, and;
3. The member has ultrasound findings consistent with in utero CMV infection or has suspected mononucleosis, and;
4. The member had negative testing for Epstein-Barr Virus (EBV).
5. Current evidence does not support the use of cytomegalovirus (CMV) nucleic acid/PCR or antigen detection tests for all other indications.

ii. <u>METAGENOMIC SEQUENCING TESTS</u>

A. Untargeted Metagenomic Sequencing Tests for Pathogen Detection
Current evidence does not support untargeted metagenomic sequencing tests for pathogen detection for all indications.

III. Notes and Definitions

A. Congenital CMV infection in a newborn can be characterized by features including rash, jaundice (yellowing of the skin or whites of the eyes), microcephaly (small head), low birth weight, hepatosplenomegaly (enlarged liver and spleen), seizures, and retinitis (damaged eye retina).

B. Ultrasound findings consistent with CMV infection may include microcephaly (smaller than normal head size), calcifications of the brain and liver, echogenic bowel, hepatosplenomegaly, various abnormalities of the brain (ventriculomegaly, intra/parenchymal cysts, abnormalities of the corpus callosum, cortical malformations), and intraventricular hemorrhages.

C. Symptoms and signs of active CMV infection can include fever, sore throat, swollen glands, extreme fatigue/malaise, mononucleosis, or hepatitis.

D. **Symptoms and signs of mononucleosis** can include malaise/fatigue, sweats, sore throat, anorexia, nausea, headache, chills, swollen glands, fever, or splenomegaly.

II. Background and Rationale

A. Cytomegalovirus (CMV) Antibody Tests

Centers for Disease Control and Prevention

"For most people, CMV infection is not a serious health problem. However, certain groups are at a high risk for serious complications from CMV infections:

1. Infants infected in utero (congenital CMV infection)
2. Very low birth weight and premature infants
3. People with compromised immune systems, such as from organ and bone marrow transplants, and people infected with human immunodeficiency virus (HIV)"

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

The following pertinent recommendations are made in the consensus guidelines:
We recommend performing donor and recipient CMV IgG serology pre-transplantation for risk stratification (strong, high).*
* In children 12 months and younger with seropositivity, nucleic acid testing may be warranted to further confirm results, as false-positives may occur due to passive antibodies transferred via breastfeeding.

American Academy of Family Physicians

"The possibility of acute CMV infection should be explored if a negative heterophile antibody test rules out EBV mononucleosis. The best diagnostic test for establishing CMV mononucleosis is serology for CMV IgM antibodies, which should be positive in the majority of patients during the symptomatic phase of the illness."

B. Cytomegalovirus (CMV) Nucleic Acid/PCR or Antigen Detection Tests

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

The following pertinent recommendations are made in the consensus guidelines:
We recommend performing donor and recipient CMV IgG serology pre-transplantation for risk stratification (strong, high).*
We recommend using QNAT calibrated to the WHO standard for diagnosis, surveillance to guide preemptive antiviral treatment, and for therapeutic monitoring due to the ability to harmonize and standardize these tests (strong, high).
We recommend when monitoring response to antiviral therapy, that QNAT is performed weekly (strong, moderate).

* In children 12 months and younger with seropositivity, nucleic acid testing may be warranted to further confirm results, as false-positives may occur due to passive antibodies transferred via breastfeeding.

Society for Maternal-Fetal Medicine

In the 2016 Consult Series #39, the SMFM recommended the following:

- Diagnosis of suspected primary CMV infection in pregnant women should be either by IgG seroconversion or with positive CMV IgM, positive IgG, and low IgG avidity (grade 1B)
- Amniocentesis is the best option for prenatal diagnosis of fetal congenital CMV infection and should be performed at >21 weeks of gestation and >6 weeks from maternal infection (grade 1C)
- Routine screening of all pregnant women for evidence of primary CMV infection is **NOT** recommended at this time (grade 1B) (p. B5)

Centers for Disease Control and Prevention

The CDC states that the standard laboratory test for evaluation of suspected congenital CMV infection is polymerase chain reaction (PCR) on saliva, with subsequent confirmatory testing on urine.

The CDC lists the following symptoms that may be present in about 10% of infants with congenital CMV:

- Rash
- Jaundice (yellowing of the skin or whites of the eyes)
- Microcephaly (small head)
- Low birth weight
- Intrauterine growth restriction (low weight)
- Hepatosplenomegaly (enlarged liver and spleen)
- Seizures
- Retinitis (damaged eye retina)
- Additionally, they list the following long-term problems that may occur in about 40 to 60% of infants born with signs of congenital CMV disease:
- Hearing loss
- Vision loss
- Intellectual disability
- Microcephaly (small head)
- Lack of coordination or weakness
- Seizures

It is important to note that some infants with hearing loss may not be detected by newborn hearing tests.

World Health Organization

The WHO defines very low birth weight as below 1.5 kg or 1500 grams, and a preterm infant as one who was born before 37 0/7 weeks of gestation. (p. vii)

UpToDate

The UpToDate article entitled “Cytomegalovirus infection in pregnancy,” includes the following list of ultrasound markers as those that are suggestive, but not diagnostic, of a fetal CMV infection:

- Periventricular calcifications
- Cerebral ventriculomegaly
- Microcephaly
- Pseudocysts, periventricular or adjacent to the occipital or temporal horn

- Hyperechogenic fetal bowel
- Fetal growth restriction
- Ascites
- Pleural and/or pericardial effusion
- Hepatosplenomegaly
- Hepatic calcifications
- Polymicrogyria
- Cerebellar hypoplasia
- Large cisterna magna
- Amniotic fluid abnormalities (oligohydramnios or polyhydramnios)
- Hydrops

C. Placental thickening and enlargement, heterogeneous appearance, calcifications"

Untargeted Metagenomic Sequencing Tests for Pathogen Detection

Gu, Miller, and Chiu

In their 2019 review, Gu, Miller, and Chiu state the following: "While the emergence of these new mNGS technologies is exciting, their rapid evolution often outpaces clinical test validation and the comprehensive collection of clinical evidence. Similar to other types of clinical testing, the application of these new diagnostic testing methods should be accompanied by rigorous clinical studies that (a) demonstrate clinical utility, (b) guide usage, and (c) uncover potential areas of misinterpretation. As with any new technology, the clinical adoption of mNGS testing will take time as providers become familiar with it and new guidelines are developed." (p. 16)

There are no professional guidelines or recommendations we identified to support the use of these tests.

III. Coding Implications

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Table 1

Criteria Sections	Lab Tests	References
Cytomegalovirus (CMV) Antibody Tests	Cytomegalovirus Antibodies (IgG, IgM)	1, 3, 4
Cytomegalovirus (CMV) Nucleic Acid/PCR or Antigen Detection Tests	Cytomegalovirus DNA, Qualitative Real-Time PCR, Saliva	1, 2, 3, 5, 7
	Cytomegalovirus (CMV), Quantitative, Plasma, PCR	
Untargeted Metagenomic Sequencing Tests for Pathogen Detection	Next Generation Sequencing Assay for Infectious Disease	6

Table 2

CPT® Codes	Description
86644	Antibody; Cryptococcus
86645	Antibody; cytomegalovirus (CMV)
87495	Infectious agent detection by nucleic acid (DNA or RNA); Clostridium difficile, toxin gene(s), amplified probe technique
87496	Infectious disease (bacteria, fungi, parasites, and DNA viruses), microbial cell-free DNA, plasma, untargeted next-generation sequencing, report for significant positive pathogens
87497	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, direct probe technique
0152U	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique
0323U	Infectious agent detection by nucleic acid (DNA or RNA; CNS pathogen next-generation sequencing

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	02/24	02/24

IV. References

1. Cytomegalovirus (CMV) and Congenital CMV Infection. (2020, August 18). Centers for Disease Control and Prevention. https://www.cdc.gov/cmv/clinical/overview.html. Accessed December 27, 2023.
2. *WHO recommendations for care of the preterm or low birth weight infant*. Geneva: World Health Organization; 2022.

3. Kotton, CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. *Transplantation*. 2018;102(6):900-931. Doi:10.1097/TP.0000000000021191
4. Taylor GH. Cytomegalovirus. *Am Fam Physician*. 2003;67(3):519-524.
5. Boppana, S and Hui, L. Cytomegalovirus infection in pregnancy. UpToDate. www.uptodate.com. Published October 5, 2023. Accessed December 27, 2023.
6. Gu W, Miller S, Chiu CY. Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection. *Annu Rev Pathol*. 2019;14:319-338. doi: 10.1146/annurev-pathmechdis-012418-012751
7. Society for Maternal-Fetal Medicine (SMFM), Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol*. 2016;214(6):B5-B11. doi:10.1016/j.ajog.2016.02.042
8. The American College of Obstetricians and Gynecologists. Cytomegalovirus, Parvovirus B19, Varicella Zoster, and Toxoplasmosis in Pregnancy Number 151. Published June 2015 (reaffirmed 2017). Accessed December 27, 2023

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a

discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.