Coding Implications
Revision Log

CONCERT INFECTIOUS DISEASE: MULTISYSTEM TESTING

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

OVERVIEW

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.

This policy is intended for use in the outpatient setting.

POLICY REFERENCE TABLE

Criteria Sections	Example Tests (Labs)	Ref
Cytomegalovirus Tests		
Cytomegalovirus (CMV) Antibody Tests	Cytomegalovirus Antibodies (IgG, IgM) (Quest Diagnostics)	1, 3, 4
Cytomegalovirus (CMV) Nucleic Acid/PCR or Antigen Detection Tests	Cytomegalovirus DNA, Qualitative Real-Time PCR, Saliva (Quest Diagnostics)	1, 2, 3, 5, 7
	Cytomegalovirus (CMV), Quantitative, Plasma, PCR (Labcorp)	
Metagenomic Sequencing Tests		
Untargeted Metagenomic Sequencing Tests for Pathogen Detection	Karius (Karius Inc)	6, 8
	Johns Hopkins Metagenomic Next Generation Sequencing Assay for Infectious Disease Diagnostics (Johns Hopkins Medical Microbiology Center)	

	Mayo Clinic Bacteria, Viruses, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid (MSCSF)	

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:

CYTOMEGALOVIRUS TESTS

Cytomegalovirus (CMV) Antibody Tests

I. Cytomegalovirus (CMV) antibody tests are considered **medically necessary** when:

   A. The member/enrollee is a prospective organ transplant donor or recipient undergoing pre-transplant evaluation, **OR**

   B. The member/enrollee has suspected mononucleosis, **AND**

      1. Had negative testing for Epstein-Barr Virus (EBV), **OR**

   C. The member/enrollee is pregnant, **AND**

      1. Has symptoms of active CMV infection, **OR**

      2. Has ultrasound findings consistent with in utero CMV infection.

II. Cytomegalovirus (CMV) antibody tests are considered **investigational** for all other indications.

back to top

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

I. Cytomegalovirus (CMV) nucleic acid/PCR or antigen detection tests are considered **medically necessary** when:

A. The member/enrollee is immunocompromised, **OR**

B. The member/enrollee is 12 months of age or younger, **AND**

1. Is a prospective organ transplant donor or recipient undergoing pre-transplant evaluation, **OR**

C. The member/enrollee is undergoing post-transplant monitoring, **OR**

D. The member/enrollee is a newborn with very low birth weight (less than 1500 grams or 3 lbs 4.9 oz), **OR**

E. The member/enrollee is a premature newborn (born before 37 weeks 0 days gestation), **OR**

F. The member/enrollee is 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**

G. The member/enrollee is pregnant, **AND**

1. Has ultrasound findings consistent with in utero CMV infection, **OR**

H. The member/enrollee has suspected mononucleosis, **AND**

1. Had negative testing for Epstein-Barr Virus (EBV).

II. Cytomegalovirus (CMV) nucleic acid/PCR or antigen detection tests are considered **investigational** for all other indications.

back to top

METAGENOMIC SEQUENCING TESTS

Untargeted Metagenomic Sequencing Tests for Pathogen Detection

I. Untargeted metagenomic sequencing tests for pathogen detection are considered **investigational** for all indications.

back to top

NOTES & DEFINITIONS

1. **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).
2. **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.
3. **Symptoms of active CMV infection** can include fever, sore throat, swollen glands, extreme fatigue/malaise, mononucleosis, or hepatitis.
4. **Symptoms and signs of mononucleosis** can include malaise/fatigue, sweats, sore throat, anorexia, nausea, headache, chills, swollen glands, fever, or splenomegaly.

back to top

BACKGROUND AND RATIONALE

CYTOMEGALOVIRUS TESTS

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 pretransplantation 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. (p. 903)

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." (p. 521)

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 pretransplantation 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. (p. 903-904)

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
- Placental thickening and enlargement, heterogeneous appearance, calcifications

METAGENOMIC SEQUENCING TESTS

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)

Casto, Fredricks, and Hill

In their 2021 review of 36 studies on Untargeted Metagenomic Sequencing for detecting pathogens in immunocompromised populations, Casto et al. focused on the clinical performance findings from 14 of these studies

The authors note that studies on clinician-ordered metagenomic next-generation sequencing for pathogen identification (mNGSpi) show that these tests had clinical impact in a small minority of cases. This discrepancy arises from differences in study designs: clinician-ordered tests are often used after other testing and treatments in difficult cases, while researcher-selected cohorts use mNGSpi earlier and on less challenging cases. Current evaluations of clinical impact, based on chart reviews and clinician reports, are subjective and potentially biased. Moreover, all studies so far lack control groups, limiting the reliability of conclusions about mNGSpi's clinical impact (p. 10-11)

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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage.

Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
86644	Antibody; cytomegalovirus (CMV)
86645	Antibody; cytomegalovirus (CMV), IgM
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
0152U	Infectious disease (bacteria, fungi, parasites, and DNA viruses), microbial cell-free DNA, plasma, untargeted next-generation sequencing, report for significant positive pathogens

back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed. Reviewed by external specialist.	11/23	02/24
Added “Lab” to policy title. Removed CPT and ICD-10 codes from policy reference table. Added CPT code table and moved the “coding implications” section.	02/24	
Corrected CPT code descriptions in CPT code table. Removed 0323U.	03/24	
Annual Review. Added policy number to header. In policy statements for the following criteria sections, changed policy to note that tests “are considered medically necessary” from the previous statement that they “may be considered medically necessary”: Cytomegalovirus (CMV)	11/24	2/25

Nucleic Acid/PCR or Antigen Detection Tests; Cytomegalovirus (CMV) Antibody Tests. For Untargeted Metagenomic Sequencing Tests for Pathogen Detection: Added Bacteria, Viruses, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid (MSCSF) (Mayo Clinic) to the Policy Reference Table and updated related background. References reviewed and updated.		

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 October 21, 2025.
2. WHO recommendations for care of the preterm or low birth weight infant. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO.
3. Kotton, Camille N. MD1; Kumar, Deepali MD2; Caliendo, Angela M. MD, PhD3; Huprikar, Shirish MD4; Chou, Sunwen MD5; Danziger-Isakov, Lara MD, MPH6; Humar, Atul MD7 on behalf of the The Transplantation Society International CMV Consensus Group. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation 102(6):p 900-931, June 2018. | DOI: 10.1097/TP.0000000000002191
4. Taylor GH. Cytomegalovirus. Am Fam Physician. 2003 Feb 1;67(3):519-24. PMID: 12588074.
5. Boppana SB, Hui L. Cytomegalovirus infection in pregnancy. In: UpToDate, Wilkins-Haug L, Hirsch MS (Eds), Barss VA (Deputy Ed), Wolters Kluwer. (Accessed October 21, 2024).
6. Gu W, Miller S, Chiu CY. Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection. Annu Rev Pathol. 2019 Jan 24;14:319-338. doi: 10.1146/annurev-pathmechdis-012418-012751. Epub 2018 Oct 24. PMID: 30355154; PMCID: PMC6345613.
7. Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. American Journal of Obstetrics and Gynecology. 2016;214(6):B5-B11.
8. Casto AM, Fredricks DN, Hill JA. Diagnosis of infectious diseases in immunocompromised hosts using metagenomic next generation sequencing-based diagnostics. Blood Reviews. 2022;53:100906. doi:10.1016/j.blre.2021.100906

back to top

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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

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.

©2023 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.