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Better testing strategies are needed for congenital CMV

By Kaisha Gonzalez, PhD

As the most common congenitally acquired viral infection and a leading cause of hearing loss in children, congenital cytomegalovirus (cCMV) is an important diagnostic test in the laboratory. In fact, cCMV is more common than the 29 other newborn conditions most often screened at birth combined.[1]

While there are numerous challenges associated with cCMV testing, two in particular stand out. First, the common transmission of CMV across all age groups means that even newborns are susceptible to infection. This complicates the distinction between postnatal infections and true congenital infections, the latter of which requires immediate medical intervention. Typically, newborns must be diagnosed utilizing samples taken within the first three weeks of life to confirm the infection is congenital. The second challenge is that about 90% of babies with cCMV are completely asymptomatic.[2-4] Anything short of universal screening for cCMV risks missing cases, yet outside of a few states that have passed legislation for widespread testing, universal screening for cCMV is beyond the scope of most healthcare facilities.

The dangers of missing cCMV cases are serious. Babies who show no symptoms of CMV infection are at risk of losing their hearing later in life.[5] Even newborns who exhibit symptoms

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LEARNING OBJECTIVES

Upon completion of this article,the reader will be able to:

1. Discuss current statistics of congenital cytomegalovirus (cCMV) that affects the newborn population.
2. List the complications that cCMV can cause later in life.
3. Differentiate between the three screening processes for cCMV and list the limitations of each.
4. Discuss current and future laboratory testing methods for the detection of cCMV.

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can sometimes evade diagnosis, as the signs of cCMV are often mild or may be missed by conventional screening methods. The implications for babies who exhibit symptoms are particularly concerning. Between 40 and 60% of these infants may experience long-lasting complications, such as cerebral palsy, cognitive impairment, and hearing or vision loss.[6] Furthermore, recent studies have uncovered a connection between cCMV infection and autism spectrum diagnoses.[7]

When early detection is possible, it offers significant benefits, as key interventions can be initiated with an accurate diagnosis. Perhaps the most important intervention is antiviral therapy, which can help mitigate future hearing loss and other complications among infected newborns.[8,9] In addition, having the correct diagnosis enables families and multidisciplinary healthcare teams to engage in routine monitoring of hearing and cCMV-related developmental milestones.

Today, expanded legislation and other advances are bringing cCMV screening to more babies, and CMV vaccine candidates are working their way through development. Improved diagnostic options, including FDA-cleared molecular assays that test saliva first and then urine, for confirmation, are now available.

Connecting the dots: Autism and cCMV

While there were already compelling reasons to diagnose cCMV infections in newborns, including the opportunity to initiate antiviral therapy and reduce the risk of hearing loss and other long-term complications, new study results linking cCMV to autism spectrum disorder (ASD) suggest even greater benefits to the early diagnosis of cCMV. The greatest benefit of early detection, particularly in light of this potential connection to autism, lies in enabling timely early intervention. Identifying cCMV within the first few weeks of life allows healthcare providers to implement individualized therapies, including speech, occupational, and behavioral services, during critical periods of brain development when they are most effective. Early diagnosis also empowers families to proactively monitor developmental milestones and seek support before delays become more pronounced later in childhood.

A study conducted by investigators at the University of Michigan and the Centers for Disease Control and Prevention (CDC) further highlights the importance of early identification.[7] In an analysis of Medicaid claims data from 2014 to 2020, researchers tracked nearly 3 million children from birth through early childhood. Within this cohort, 1,044 children were diagnosed with cCMV, and notably, 49% of these children also had a diagnostic code associated with autism-related symptoms.

After adjusting for sex, region, and birth year, the study found that children diagnosed with cCMV were more likely to later receive an autism diagnosis compared to their peers without CMV. The authors noted that future research should focus on populations identified through newborn screening for cCMV, as the current study likely captured children who were diagnosed because they were already symptomatic.

Overall, these findings reinforce that early diagnosis of cCMV not only offers an opportunity to address known complications but may also open new pathways to support cognitive and developmental outcomes, particularly if a heightened risk for autism is confirmed through broader studies.

Screening strategies: Targeted, expanded, and universal models

Clearly, testing for congenital cases of CMV infection is important. However, consensus around the need to test has not translated into agreement on how to test. Currently, there are three primary models for cCMV screening practices: targeted hearing screening, expanded targeted screening, and universal screening.

Historically, targeted hearing screening has been the standard practice in healthcare. In this approach, cCMV testing is performed only when a newborn fails the universal newborn hearing screen. While this strategy may seem practical given the well-established link between cCMV and hearing loss, it is neither particularly efficient nor effective. It is the lowest-cost option, as it limits testing to a smaller subset of infants, but comes at a significant cost. Many newborns with cCMV pass their hearing screen; however, studies have shown that standard newborn hearing screening can miss up to 43% of infants with sensorineural hearing loss or congenital CMV infection.[10] As a result, normal hearing results can delay diagnosis in infected infants, reducing the opportunity for early intervention and increasing the risk of long-term developmental complications.

The second approach, expanded targeted screening, builds on the initial model by addressing some of its key limitations. In this strategy, cCMV testing is performed not only based on failing newborn hearing screen but also based on those with known risk factors such as premature birth or maternal CMV infection during pregnancy. Additional clinical signs including low birth weight, hepatosplenomegaly, microcephaly, and petechiae can also be incorporated into the screening algorithm. While this model involves testing more infants by expanding the targeted screening, it remains cost-effective by focusing on only on the babies with an increased probability of infection.

Expanded targeted screening offers broader case detection and helps reduce the number of missed infections, increasing the likelihood that affected infants can benefit from timely intervention. However, this approach still risks overlooking asymptomatic cCMV cases and can be more challenging to implement. It requires clear guidelines to define qualifying risk factors, and in practice, some of these clinical judgments may be more subjective.

The final approach, universal screening, represents the broadest strategy: testing all newborns for cCMV shortly after birth. While this method is the most comprehensive, it is also the most expensive and least efficient in terms of resources. Its key advantage lies in its ability to detect cases regardless of symptoms, ensuring that no infected infant is overlooked. When the goals are health equity and reducing the risk of long-term complications, universal screening offers the most significant potential benefit.

However, high costs limit its adoption across states and healthcare systems. Additionally, limited evidence supports the use of antiviral therapy for asymptomatic infants, further reducing the perceived value of this approach. If universal screening is implemented, the choice of testing method becomes critical. Some assays and sample types have lower sensitivity, which may undermine the effectiveness of widespread screening by failing to identify true cases.

A retrospective study conducted at Seattle Children's Hospital examined clinical, laboratory, and imaging data from infants diagnosed with cCMV between 2009 and 2021.[11] Researchers evaluated the effectiveness of various screening strategies by applying each model to a cohort of 112 confirmed cases.

While universal screening would have identified 100% of infections, targeted hearing screening alone would have detected only 66% of cases and an expanded targeted screening approach, which incorporates additional clinical risk factors, would have captured 92%.

In addition to the primary screening strategies described above, some healthcare systems are piloting a focused approach: cCMV screening for infants admitted to the neonatal intensive care unit (NICU). The rationale behind this strategy is that NICU patients, often preterm or critically ill, may have a higher likelihood of congenital infections including cCMV. Systematically testing this high-risk population may increase the detection of symptomatic cases that might otherwise be missed.

This approach also addresses a gap in routine newborn screening practices. Infants in the NICU often do not undergo a standard hearing screening at the same time as healthy newborns, and automated hearing tests are not recommended for high-risk infants born before 34 weeks of gestation.[12] As such, dedicated NICU screening protocols offer an opportunity to identify cCMV cases that might fall outside the scope of traditional screening timelines.

Policy and progress: Where legislation is leading the way

While expanded targeted screening strategies can be implemented at the discretion of individual healthcare systems, universal cCMV screening typically requires legislative action at the state level. Although not yet standard practice nationwide, several states have recently made progress toward broader implementation.

In 2021, Minnesota became the first state to pass legislation mandating universal cCMV screening for all newborns.[13] Connecticut is slated to become the second state to adopt the universal program beginning in 2025. Similar legislation has been proposed but not yet enacted in Indiana, Massachusetts, Michigan, Mississippi, New Hampshire, New York, and Oregon.[13]

At the federal level, the National CMV Foundation submitted a nomination in 2019 to include cCMV in the Recommended Uniform Screening Panel (RUSP). If approved, this designation would support the adoption of universal screening in states that align their programs with federal guidelines.

Beyond expanding access to testing, legislative initiatives play a crucial role in raising awareness about the impact congenital CMV has upon healthcare systems. Despite being the most common congenital infection in the United States, public and provider awareness remains low. Increased visibility through policy efforts can help improve education, promote early detection, and ultimately reduce the long-term effects of undiagnosed cCMV.

Diagnostics in practice: Molecular methods and specimen selection

Regardless of the screening strategy adopted, clinical laboratories are responsible for selecting the most appropriate method for detecting cCMV. Given the critical three-week window for confirming a diagnosis of cCMV, timely testing is essential. Traditional methods like viral culture are too slow to meet this clinical need, making rapid, high-sensitivity molecular assays the preferred choice for early and accurate detection.

The ideal diagnostic test for cCMV would deliver rapid results with high sensitivity and specificity. Molecular testing meets these criteria and is widely regarded as the most appropriate method for cCMV screening. PCR-based assays offer excellent analytical sensitivity and can provide results within hours, facilitating timely diagnosis within the critical three-week window. When performed on automated, sample-to-answer platforms, these assays also require minimal hands-on time, enabling laboratories to efficiently scale testing capacity to meet clinical demand.

An important consideration when selecting a diagnostic test for cCMV is the range of sample types the test can accommodate. Dried blood spots (DBS) collected on Guthrie cards offer logistical advantages for retrospective analysis and integration with existing newborn screening workflows. However, recent findings indicate that DBS-based testing continues to fall short of optimal sensitivity thresholds.

In two independent laboratories, DBS testing yielded sensitivities ranging from 73% to 77%, with a combined sensitivity of 86% across both sites.[14] These figures indicate that there is a variability of reliable results and suggest that a meaningful number of cCMV cases may still go undetected when relying solely on DBS samples. Further complicating its utility, the DBS-based cCMV test currently used in Minnesota is not FDA-cleared and still relies on manual card punching, an approach that introduces workflow inefficiencies and increases the potential for human error. While DBS remains convenient for certain public health applications, it is not considered suitable for definitive diagnosis, as a negative result cannot reliably exclude infection.[14,15]

In contrast, saliva swabs and urine samples are widely recognized as more reliable for accurate detection and are the preferred specimens recommended in clinical guidelines for cCMV diagnosis. Saliva samples are easier to collect and are often used as the initial screening specimen. However, due to the potential for contamination from breast milk leading to false positives, many clinical laboratories confirm positive saliva results with follow-up urine testing, which provides higher specificity.[16] As such, it is essential to select a molecular assay that is validated or FDA-cleared for use with both saliva and urine to ensure accurate and guideline-compliant diagnostic workflows.

Looking ahead: The promise of CMV vaccines

Perhaps the most promising long-term solution would be the development of an effective CMV vaccine, which could significantly reduce the incidence of cCMV and diminish the need for widespread screening strategies. Studies have shown that prompt identification and response to CMV infection during pregnancy can help prevent vertical transmission to the fetus.[17] Although no vaccine is currently available, several candidates are in development.

Vaccine platforms under investigation include vectored CMV genes, replication-defective viral strains, and recombinant strains derived from wild-type virus.[1] Other approaches involve DNA plasmids, self-replicating RNA, peptides, and virus-like particles. In some cases, these candidates have already demonstrated immunogenicity and safety in early-phase trials. Development efforts are ongoing across both academic institutions and major pharmaceutical companies.

Putting it all together: The case for improved screening models

Given the potentially severe and lifelong health consequences of undetected congenital cCMV infection, including sensorineural hearing loss, neurodevelopmental delay, and motor

or vision impairment, it is critical that clinical laboratories implement an effective screening strategy to identify affected infants early. Whether through one of the established models or a customized approach tailored to specific risk factors or patient populations, the primary objectives should be to reduce the number of missed cases and to enable timely intervention. Screening strategies should emphasize the use of sensitive, rapid molecular assays validated for high-yield sample types such as urine and saliva, which are preferred due to their superior viral load profiles during the neonatal period.

Although universal screening offers the highest sensitivity for detecting all cCMV cases — symptomatic and asymptomatic — its broad implementation may be limited by cost, logistical complexity, and reimbursement constraints. In contrast, expanded targeted screening may offer a more feasible alternative, balancing improved case detection with economic and operational practicality. By incorporating a broader set of clinical risk factors beyond failed hearing screens, this approach increases the likelihood of identifying infected infants while staying aligned with the resource capacities of healthcare systems.

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