

# An Ethical Analysis of Newborn Congenital Cytomegalovirus Screening

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Congenital cytomegalovirus (cCMV) affects approximately 1 in every 200 US infants and can be associated with long-term neurodevelopmental sequelae, including sensorineural hearing loss, cerebral palsy, and intellectual disability. As cCMV is infrequently diagnosed based on clinical suspicion alone, newborn cCMV screening programs have been gaining traction, especially hearing-targeted programs which only test infants who fail their newborn hearing screen. cCMV screening programs raise unique ethical dilemmas of both under- and over-diagnosis of cCMV. In this Ethics Rounds, we present a case in which the parents of a child with symptomatic cCMV that was not recognized until 4 years of age urge the birth hospital to implement a cCMV screening program. We then ask a parent-clinician, a medical ethicist and pediatrician, and a primary care pediatrician to comment on how they would advise the hospital administration and consider the ethical and clinical implications of a cCMV screening program. The commentaries herein arrive at differing conclusions about cCMV screening. The first highlights the developmental advantages of early cCMV detection, supporting a broad approach to treatment beyond antiviral medication alone. The second explores cCMV screening from the perspective of newborn screening as a public health program, noting shortcomings in available testing platforms, and raising concerns about overdiagnosis and overtreatment. The final commentary challenges the risks of undue parental anxiety and vulnerable child syndrome as a barrier to screening, instead considering cCMV screening as a controlled opportunity to understand and support the experiences of affected children and their families.

Congenital cytomegalovirus (cCMV) is a common congenital infection, affecting approximately 1 in every 200 live born infants in the United States, and can be associated with neurodevelopmental sequelae such as sensorineural hearing loss (SNHL), cerebral palsy, and intellectual disability.<sup>1-3</sup> Symptomatic cCMV refers to the 10% of infants who present with signs, laboratory or cranial imaging abnormalities in the newborn period, and they often have most disabling long-term sequelae. The remaining 90% of infants are born with asymptomatic cCMV, having no signs at birth. Asymptomatic infants are largely

thought to have typical developmental outcomes except for inner-ear related sequelae.<sup>4</sup> Of those with asymptomatic cCMV, 10% to 20% will develop SNHL and 35% to 50% will develop vestibular and balance disorders in childhood.<sup>4,5</sup> Due to its often subtle presentation at birth, most (95% to 99%) of cases of cCMV go undiagnosed in the absence of a screening program, leading to missed opportunities for early hearing intervention, close developmental monitoring, as well as antiviral medication for those with severe disease.<sup>6,7</sup> As such, cCMV newborn screening (NBS) programs have become more prevalent in the

## abstract

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United States, but not without controversy.<sup>8-10</sup>

There is much debate about the methods and merits of cCMV NBS, including which infants to screen, what test to use, and whether the benefits of early detection and intervention outweigh the risks.<sup>8,11-13</sup> In terms of cCMV screening methods, hearing-targeted (HT) newborn cCMV screening programs are the most common (as opposed to universal screening programs), and limit cCMV screening to infants who fail their newborn hearing screen (NBHS).<sup>8</sup> Early detection of SNHL with intervention to promote spoken (eg, hearing aids or cochlear implants, auditory-verbal therapy) or signed (eg, American Sign Language) communication have been robustly associated with improved long-term outcomes in children with hearing loss in general.<sup>14-16</sup> Whereas HT cCMV screening can lead to the early diagnosis and treatment of a minority infants with cCMV, most (93%) infants with cCMV do not fail their NBHS and, as such, are not identified.<sup>10</sup> This includes almost half (43%) of newborns who will develop cCMV-associated SNHL in infancy, because of the often fluctuating and rapidly progressing nature of cCMV-related SNHL.<sup>10</sup> On the other hand, universal screening identifies all infants with cCMV, in theory, including those with symptomatic disease, those who will develop hearing loss in infancy, and all of those (upwards of 80%) who will never develop disabling long-term sequelae.<sup>17</sup>

Newborn screening for cCMV can be performed using urine, saliva, or dried blood spot polymerase chain reaction (PCR) testing; each has advantages and challenges.<sup>18</sup> Specimens for cCMV testing need to be collected before 21 days of life to distinguish between congenital and acquired postnatal infection.<sup>11</sup> Urine

cytomegalovirus (CMV) PCR is both sensitive and specific (98% to 99%) yet is challenging to collect in the days after birth because of physiologic low urine output in newborns.<sup>19-22</sup> Saliva CMV PCR is somewhat less sensitive and specific (92% to 98%, and 92% to 99%, respectively) because of false-positives (0.03% to 0.1%) from CMV shedding in breastmilk.<sup>19,21,23,24</sup> As such, saliva specimens must be collected at least 30 minutes after breastmilk consumption, and any positive result should be confirmed with a urine PCR.<sup>25</sup> To date there are no commercially available high-throughput urine or saliva CMV PCR assays in the United States. Lastly, single primer PCR testing for CMV in dried blood spots has variable sensitivity (between 38.3% to 76.8% in published reports).<sup>18,26,27</sup>

Targeted treatment of cCMV is limited to the use of valganciclovir in the most severely affected infants.<sup>11</sup> Current expert recommendations are based on a randomized controlled trial of a 6-month (versus 6-week) course of valganciclovir treatment of infants with moderate-to-severely symptomatic cCMV which found no difference in short-term hearing outcomes but found modest improvements in development and hearing outcomes at 24 months in those who received an active drug for 6 months.<sup>28</sup> However, during the first 6 weeks of open-label valganciclovir treatment, 19% of the study participants developed transient grade 3 to 4 neutropenia.<sup>28</sup> Although there was no difference in rates of neutropenia from 6 weeks to 6 months between the placebo (27%) and the active drug group (21%,  $P = .064$ ),<sup>28</sup> and other work has reported lower rates of grade 3 to 4 neutropenia (~6%),<sup>29</sup> experts caution against overuse of valganciclovir.<sup>11,12,30</sup> Other adverse events reported

include anemia, thrombocytosis, and hepatitis.<sup>29</sup> The safety and efficacy of valganciclovir use in infants with asymptomatic cCMV are under investigation in ongoing clinical trials,<sup>31-</sup> although smaller studies have shown mixed results.<sup>33-35</sup> As such, expert recommendations groups have yet to reach full consensus about the use of valganciclovir in infants with mildly symptomatic or asymptomatic cCMV with isolated SNHL.<sup>11,12,33</sup>

We present a case in which a cCMV screening program is being considered by the administration of a children's hospital and explore the ethical and clinical implications of cCMV screening policies.

#### THE CASE

A 4-year-old girl was referred for audiology testing because her school's observation that she positioned her head and body to orient her left ear toward the teacher. She was born at 36 weeks gestational age and was well-grown. Her postnatal course was unremarkable; she was cared for in the newborn nursery, had no remarkable findings on physical exam, and nursed well. She failed her NBHS bilaterally. Per hospital protocol, she was scheduled for follow-up hearing testing at 4 weeks, which she passed bilaterally; therefore, no further workup was pursued. The girl attained gross motor and speech and language milestones just outside of the typical range (eg, walking at 16 months, first words at 14 months).

Audiology testing now reveals right-sided profound SNHL and a left-sided mild loss. Genetic tests for hearing loss-associated variants are ordered over the following months and are negative. Small cysts and trace calcifications in her brain parenchyma are incidentally found

on brain imaging conducted as part of a cochlear implant evaluation. Her newborn dried blood spot is tested for CMV and returns as positive, confirming the diagnosis of cCMV. Upon subsequent consultation with pediatric infectious disease specialists, the family is told that antiviral treatment is unproven to be beneficial in older children but may have improved outcomes had she been treated as an infant.

Her parents contact the birth hospital administration, asking why their daughter was not tested for cCMV at birth when she failed her NBHS. They have learned that such programs are in place at other health systems. In response, an internal committee is convened to determine whether a cCMV screening program should be implemented at the hospital.

#### **MEGAN H. PESCH, MD, MS, DEVELOPMENTAL AND BEHAVIORAL PEDIATRICIAN, AND PARENT, COMMENTS**

The child in this case has severe symptomatic cCMV, owing to her intracranial lesions.<sup>11</sup> Had a cCMV screening program been in place at the time of her failed NBHS, she would have been diagnosed and eligible for antiviral treatment, which may have slowed or halted the progression of her SNHL.<sup>11,28</sup> As the parent of a child with cCMV, I can empathize with the heartache that comes with a late diagnosis, and the accompanying “what ifs” that can never be answered. As a clinician, I can now look back at my daughter’s early infancy with 20:20 hindsight and appreciate the systemic factors and knowledge gaps (including my own) that contributed her late diagnosis, many of which likely explain the under-diagnosis of cCMV in this country. I share the lessons I have learned over the last 3 years, and perspectives as a parent and

clinician which have led me to believe that newborns should be universally screened for cCMV.

1. Most infants with cCMV go undiagnosed in the absence of a screening program. This includes 90% of those with symptomatic disease,<sup>7</sup> most of whom do not present with the classic “blueberry muffin” rash that I memorized while studying for my boards.<sup>17</sup> Clinicians simply cannot see outward signs cCMV in most infants, yet invisible sequelae such as intracranial involvement, hepatitis, and SNHL may not be apparent until further evaluation, which cannot happen without screening. A missed early diagnosis means a missed opportunity for intervention and holistic treatment.
2. Asymptomatic cCMV is not entirely asymptomatic. Infants with asymptomatic cCMV may develop important sequelae, such as neonatal or childhood onset SNHL (15% to 25%) and vestibular and balance disorders (45%).<sup>5,36</sup> The term “asymptomatic” implies no symptoms which may offer false reassurance to providers and parents. The knowledge that an infant has a 10% to 20% chance of developing SNHL can inform a proactive, versus reactive, approach to hearing loss.<sup>37</sup> Research supports parents’ desire to know if their infant has cCMV, even if that infant is asymptomatic, and never develops sequelae.<sup>38–40</sup> Provider communication and family education are critical to lowering parental anxiety, which is an inherent risk of any screening test.<sup>41</sup>
3. Treatment is available for all infants with cCMV, and is not limited to antiviral medication,

as I once thought. Experts advise limiting antiviral treatment to the most severely affected infants, which make up <10% of all cases. Yet when a child is diagnosed with cCMV, there is an undeniable urge as a parent or provider to “do something,” which may result in over-prescription of valganciclovir, especially if it is described as the only treatment option.<sup>28,29</sup> Treatment of cCMV should be approached as a holistic set of interventions to mitigate possible neurodevelopmental sequelae. These can include hearing monitoring, early hearing amplification if a loss is identified, sign language acquisition, speech therapy, physical therapy, parental social support, and developmental monitoring. In general, the benefit of early detection and intervention for infants at increased risk of neurodevelopmental delays has been robustly demonstrated and is a cited motivation for Part C of the Individuals with Disabilities Education Act.<sup>42,43</sup> A broad approach to treatment inclusive of anticipatory monitoring and therapy may lessen inappropriate use of antiviral medications and in better long-term outcomes for all.

4. Hearing-targeted screening falls short and fails to identify most infants with cCMV (93%), including 43% of those with cCMV-associated SNHL in infancy, and 62% of those with symptomatic disease who may be eligible for antiviral treatment.<sup>10</sup> cCMV-associated SNHL can present at birth, fluctuate (as in the case), progress gradually, progress rapidly, or have an onset years later.<sup>44</sup> A failed NHBS is not a

sensitive indicator of cCMV or cCMV-associated SNHL. To adequately identify infants with cCMV-associated SNHL, universal screening is necessary.

I sometimes wonder about the infants affected by cCMV that I did not recognize during my early career, including my own daughter, who may have been caught with universal screening. Yet, I suspect like many providers, cCMV was not emphasized in my training. cCMV needs to be prioritized by professional organizations, health systems, and federal funding agencies as a condition worthy of early detection and intervention. I believe that universal cCMV screening would result in improved outcomes for those affected, but only if pediatric providers are equipped with the necessary knowledge, support, and clinical guidance to care for these infants and their families. Longitudinal, population-based studies are currently underway and promise to help answer debated questions about long-term outcomes, and “net benefit” of cCMV screening.<sup>18,31</sup> Yet, whereas the researcher in me awaits this data, the mother-pediatrician in me knows that opportunities for early cCMV intervention cannot wait.

**LAINIE FRIEDMAN ROSS, MD, PHD,  
ETHICIST AND PEDIATRICIAN,  
COMMENTS**

In 2001, the Health Resources and Services Administration’s (HRSA) Maternal and Child Health Bureau commissioned the American College of Medical Genetics (ACMG) “to convene an expert panel to outline a process of standardization of outcomes and guidelines for state newborn screening programs, including a recommended uniform panel (RUSP) of conditions to include in state newborn screening

programs.”<sup>45</sup> The HRSA and ACMG Committee developed a list of 80 metabolic and genetic conditions and 3 infectious diseases (CMV, HIV, and Toxoplasmosis) for consideration. In 2005, the HRSA and ACMG report recommended a panel that included 29 conditions and 25 secondary conditions, but did not include any of the infectious diseases,<sup>46</sup> which is not surprising given the fact that the HRSA and ACMG committee did not include anyone with an infectious disease background. Fifteen years later, whereas the RUSP has expanded beyond the blood spot to include NBHS and critical congenital heart disease screening, there is still no infectious disease included in the RUSP, and only a few states screen for any infectious conditions.<sup>47</sup>

From a public health perspective, I understand why cCMV was not included in the RUSP in 2005. Although CMV is the most frequent infectious cause of neonatal SNHL and other developmental problems, adoption of a condition for inclusion in the NBS panel must meet strict public health screening criteria. Although not designed specifically for NBS, the Wilson and Jungner criteria for population health screening were developed in 1968 for the World Health Organization and applied to NBS conditions in the United States and internationally.<sup>48</sup> These criteria continue to be used with modifications in various countries.<sup>49,50</sup> In the United States, the Advisory Committee on Heritable Diseases in Newborns and Children uses their own detailed set of criteria.<sup>51</sup> All these criteria require an acceptable screening test which cCMV failed to meet in 2005 and still fails to meet in 2022 given the current NBS laboratory infrastructure.

The best assay for diagnosing CMV infection using the current Guthrie filter-paper card is by PCR. PCR on

NBS blood spots was first incorporated as a first line population-based screening test in 2010 when severe combined immunodeficiency screening was added to the RUSP,<sup>45</sup> but PCR testing for CMV in blood spots has variable sensitivity.<sup>18,26,27</sup> PCR screening for cCMV has greater sensitivity with urine or saliva, but urine samples are hard to collect in the first days of life and saliva has a high false positive rate because it must be timed separate from breastfeeding. Even more significant is that a swab would require a major overhaul of public health departments which have been structured to collect and conduct screening on filter-paper.

If the inclusion of cCMV in the RUSP is not yet ready for prime time, an alternative option would be to support HT cCMV screening. HT cCMV screening would only be conducted on those children who fail NBHS, and the testing will be done in private laboratories rather than in state public health department.

The idea of targeted screening is not new. NBHS itself began as a targeted measure. Before 1994, only infants with specific risk factors for hearing loss were screened at birth, although over 50% of children with hearing loss had none of these risk factors.<sup>52</sup> To screen infants who fail a hearing test for cCMV is a start, because if SNHL is identified early, treatment with antiviral agents begun in the first month has been shown to improve audiologic outcomes at 6 months, although long-term benefits wane over time and are less significant which reduces the benefit to risk calculation of valganciclovir.<sup>28</sup> More importantly, “[t]he majority of newborns who fail NBHS at birth and also have positive cCMV test results will go on to have neither hearing loss nor any sequelae of

cCMV.”<sup>53</sup> This again challenges the benefit to risk calculation of valganciclovir, particularly given that safety and efficacy in those with milder presentations have not been well-established.<sup>12,54</sup>

Although HT cCMV screening will miss many with cCMV who are asymptomatic at birth,<sup>10,36</sup> it is already mandated and implemented in 6 states, Connecticut, Iowa, New York, Utah and Virginia, although only Iowa and Utah require CMV testing in the first 21 days.<sup>56</sup> And yet, even in these states, the effectiveness of HT cCMV will not be fully realized because public health departments are not required, nor do they have the staffing or resources, to collect long-term outcome data. As such, the hearing outcomes of most children with cCMV will not be captured, and the necessity and effectiveness of diagnosis and treatment will not be clearly determined.

As a pediatrician I am sympathetic toward the family’s desire to reduce preventable SNHL in children, but I worry about the harms we may cause by overidentification and overtreatment. Data from the states that implement universal NBS and/or HT cCMV screening will help determine whether other states should follow suit.

#### **PHOEBE DANZIGER, MD, PRIMARY CARE PEDIATRICIAN, COMMENTS**

If this family were part of my rural, community-based general pediatrics practice, I would share in their frustration regarding her delayed diagnosis and the missed opportunities for antiviral therapy in infancy as well as for more robust developmental surveillance and potentially earlier access to hearing interventions, such as hearing amplification and/or cochlear implant.

Knowledge and awareness of cCMV has expanded greatly in recent years, but clinician education and practices have not kept pace. Whereas some physicians who care for newborns are aware that an initial failure on newborn hearing screening is associated with an elevated risk of cCMV, even if repeat screening is normal, many are not.

If I were counseling this family in my practice, I would not be able to offer them a coherent explanation for why the approach to cCMV screening and diagnosis in the United States remains so haphazard. Drs. Pesch and Ross offer compelling arguments both for and against targeted and universal cCMV screening; from a primary care perspective, I am strongly in favor of implementing either screening approach, as I believe that a standardized cCMV screening program would reduce the risk of children “slipping through the cracks,” and would allow for an organized and robust study following implementation, with the opportunity for further refinement based on the results.

My practice catchment area is characterized by high levels of poverty, low health literacy, and a shortage of pediatric clinicians; many children do not present for developmental surveillance at the recommended intervals. If cCMV screening and detection protocols were standardized and regulated at the county or state level, this would help to identify and track children at higher-than-average risk and would provide an additional layer of support to overburdened pediatric clinicians with the goal of ensuring that appropriate follow-up occurs for every newborn.

In a recent article, Gievers et al present several common arguments against targeted cCMV screening.<sup>53</sup> The authors argue, for example, that

the risk of a cCMV screening program causing “vulnerable child syndrome” outweighs the benefits of a targeted screening program, and that targeted cCMV screening does not clearly meet criteria for an effective screening test.<sup>53</sup> Concerns have also been raised about the possibility that cCMV detection will lead to nonbeneficial or even harmful treatment.

Whereas these concerns are valid, it is patronizing to assume that we know how all parents would respond to screening results, and to preemptively determine that parents and clinicians alike will be unable to interpret and react to cCMV screening results thoughtfully and intelligently. Whereas knowledge is not always power, as is evident from some of the challenges presented by direct-to-consumer genetic testing, studies have shown that most parents are in favor of early cCMV diagnosis and have found that information useful.<sup>38–40</sup> If the primary rationale for opposing either targeted or universal cCMV screening is the fear that parental distress and the potential that identified infants may receive nonbeneficial or harmful treatment, I do not believe this provides sufficient ethical justification for forgoing cCMV screening given the substantial benefit that some infants would likely receive from cCMV detection.

With respect to the criticism that cCMV screening may not align with the characteristics of an effective screening test, I am concerned that if we fixate too narrowly on such criteria, we will miss sight of the more holistic impact that cCMV screening may have on children and their families. In their article on newborn screening, van der Burg and Oerlemans describe the distinction between “hard impacts,” such as health, and “soft impacts,” such as psychosocial benefit or

harm.<sup>56</sup> The authors go on to observe that although hard impacts are considered worthy of policy consideration, soft impacts tend to be relegated to the private domain, where parents (often mothers) are left alone to shoulder the burden. It would behoove us to consider whether implicit bias and deeply ingrained cultural tropes such as the “anxious” or “hysterical” mother may be influencing what is purported to be a purely objective public health policy decision.

Rather than shy away from the potential psychosocial impact on families, we should consider whether standardized cCMV screening might, in fact, offer a more controlled opportunity to understand and support the experiences of children and parents. It behooves us to at least imagine the ways in which ethics and values, such as the importance of patient and family-centered care and robust, proactive support for children with developmental differences and disabilities, can be manifested and bolstered through public health policy. Thus, rather than asking whether cCMV screening is “worthwhile,” or “does more harm than good,” I suggest that we reframe our inquiry as follows: how might targeted or universal cCMV screening empower parents, clinicians, and society to help young children and their families thrive?

#### OUTCOME OF THE CASE

Clinicians in the newborn nursery, audiology, and pediatric otolaryngology expressed support for a HT cCMV screening protocol as a preliminary step toward broader targeted screening in the future (eg, microcephaly, small-for-gestational age, preterm birth <35 weeks gestational age etc.). The director of the microbiology laboratory expressed concerns about training staff to use new equipment necessary

to run in-house saliva CMV PCR testing. As such, the hospital was limited to the use of urine specimens, which were challenging to collect and required processing at an outside facility. As a stopgap measure, the hospital began systematically screening infants who failed their repeat NBHS as an outpatient, with plans to expand screening to the newborn nursery when a new CMV PCR assay compatible with the existing equipment in the microbiology laboratory, was released later that year.

#### ARMAND H. MATHENY AN TOMMARRIA, MD, PHD, SECTION EDITOR, COMMENTS

The commentators present the potential benefits and detriments of HT and universal newborn cCMV screening. The benefits, especially when considered holistically, are such that screening deserves serious consideration and HT cCMV screening has been implemented in some health systems and states. The benefits and risks do not, however, clearly justify including universal cCMV screening in the RUSP. Additional research is needed and is ongoing. The different ways in which the commentators weigh the potential benefits and risks raise the following question: should testing be offered to parents as part of shared decision making? Different parents and their healthcare providers may come to different conclusions about testing their own neonates based on their values. Having asked this question, I acknowledge the additional work this would require of providers and clinical laboratories. It will therefore be important to develop clinician and parent education and decision aids to support the care of patients with cCMV as it continues to evolve.

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#### ABBREVIATIONS

ACMG: American College of Medical Genetics  
cCMV: congenital cytomegalovirus  
CMV: cytomegalovirus  
HT screening: hearing targeted cCMV screening  
HRSA: Health Resources and Services Administration  
NBHS: newborn hearing screen  
RUSP: recommended uniform panel  
SNHL: sensorineural hearing loss

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