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Should Hearing Targeted Screening for Congenital Cytomegalovirus Infection Be Implemented?

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Abstract

Since 2013, after Utah became the first state to implement hearing targeted early CMV screening, a national debate has been percolating about whether this approach should be introduced nationally. Currently Utah, Iowa, Connecticut, and New York have passed legislation mandating early CMV screening, and over 100 birth hospitals across the United States have voluntarily implemented early CMV screening programs as part of their standard of care. We reviewed the evidence related to this approach and used the Wilson and Jungner (1968) criteria to evaluate this method of screening. Based on these criteria, there is substantial rationale and evidence to support a hearing targeted approach to screen for congenital CMV. Given this evidence, we currently recommend that infants who fail newborn hearing screen should undergo CMV screening.

Keywords

cytomegalovirus; sensorineural hearing loss; universal newborn hearing screening

1. Introduction:

Congenital cytomegalovirus (cCMV) is the most common congenital infection worldwide. It is also the number one cause of non-genetic sensorineural hearing loss (SNHL) and a leading cause of central nervous system defects in newborns [1–3]. While patients and their families directly experience devastating speech and language delays associated with this disease, cCMV infection is also responsible for a massive economic burden on society of nearly 4 billion dollars annually. This cost predominantly stems from the long-term cognitive and hearing impairments experienced by these patients [4, 5].

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The antiviral drug, valganciclovir will be discussed in this manuscript. This drug is not FDA approved for the treatment of children with congenital cytomegalovirus infection.

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Prevalence of cCMV varies by population, but is believed to be 0.58% overall (0.41–0.79 95% CI) [6]. In 2018, approximately 20,000 infants were estimated to have been infected with cCMV in the United States. Ten percent of newborns with cCMV present with symptomatic infection at birth, but the majority (90%) of cCMV infected infants are asymptomatic. The definition of a symptomatic infection varies between different authors. Certain researchers and clinicians have included SNHL in this category, while others have not. For the purposes of this paper, we define symptomatic disease to include evidence of thrombocytopenia, petechiae, hepatosplenomegaly, intrauterine growth restriction, hepatitis, central nervous system involvement, or chorioretinitis. We separate those with isolated SNHL as a distinct category, designated as asymptomatic cCMV infected patients with isolated SNHL. Asymptomatic disease is defined by those with a normal physical examination. These categories are somewhat artificial and most likely represent a spectrum of disease severity. Ronchi et al (2020) reported that 56% apparently asymptomatic infants had laboratory or neuroimaging abnormalities, which prompted antiviral therapy in certain cases. Goderis et al (2014) reviewed 37 studies on children with cCMV and noted that in an asymptomatic cohort, between 9.4–16.3% either present with, or develop SNHL over time. As this group lacks overt signs of infection, patients with CMV-induced SNHL who are otherwise asymptomatic are at risk for a delayed diagnosis. Delay in diagnosis and initiation of intervention puts children at increased risk for speech, language and learning delays [7–9]. Addressing hearing loss at the earliest age possible allows for auditory, education, speech and potentially medical intervention while the child is still in early stages of development [8, 9].

We have previously shown that CMV testing for idiopathic SNHL can be done successfully and at low cost [10]. This approach is somewhat complicated however, as testing is time sensitive. Testing needs to performed before the infant is 3 weeks of age, as a later positive result may reflect postnatal infection which is not associated with SNHL[11]. A simpler approach would be to perform CMV testing for any infant who fails the newborn hearing screen before 3 weeks of age. This process would tie directly into universal newborn hearing screening, an existing program with proven success in discovery of infant hearing loss. This hearing targeted CMV screening (HT-CMV) approach was implemented for the first time state-wide in Utah in July 2013. Since then, a number of states have mandated HT-CMV screening [12].

In weighing the decision to designate HT-CMV screening as an established medical practice, the risks and benefits to the patient, family and society at large must be considered. In 1968, Wilson and Jungner published “Principles and Practice of Screening for Disease”, a seminal work that has been used to guide screening decisions to this day. The authors noted that “The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement is far from simple though sometimes it may appear deceptively easy [13].” The principles of screening are defined by the following 10 criteria: (1) the condition sought should be an important health problem; (2) the natural history of the condition, including development from latent to declared disease, should be adequately understood; (3) there should be a recognizable latent or early symptomatic stage; (4) there should be a suitable test or examination; (5) the test should be acceptable to the population; (6) there should be an agreed policy on whom to treat as patients; (7) there should be an

accepted treatment for patients with recognized disease; (8) facilities for diagnosis and treatment should be available; (9) the cost of case-finding should be economically balanced in relation to possible expenditure on medical case as a whole, and (10) case-finding should be a continuing process and not a "once and for all" project. Given the potential significant implications of HT-CMV screening, especially if started on a national basis, we decided to examine the merits of this approach using the 10 criteria from Wilson and Jungner (1968).

2. Wilson and Jungner Criteria for Newborn Screening

2.1 Important Health Problem:

As presented earlier, the incidence of cCMV (6 per 1000 newborns) is extremely high. Ronchi et al. (2017) describe cCMV as "a huge public health problem," as this number translates to over one million newborns globally [14]. This prevalence is higher than the 1.5 per 1000 incidence for all metabolic, endocrine, hematologic and functional disorders combined, based on a panel of 29 disorders recommended in 2006 for universal newborn screening [15]. These numbers are also higher than many of the 35 core disorders that undergo screening based on guidance from the Recommended Uniform Screening Panel promulgated by the Secretary of the Department of Health and Human Services (https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html).

2.2 There must be a recognizable latent or early symptomatic stage.

Congenital CMV fits the classic disease model for screening, as SNHL is typically preceded by a lengthy asymptomatic phase. Several studies support the importance of identifying the preclinical phase since it provides a rationale for surveillance, audiologic testing, and the opportunity to promptly identify late onset SNHL[10, 16, 17]. Diagnosis will also obviate the need for costly testing and a potentially lengthy period ruling out other potential causes of SNHL[18]. The potential role of antiviral therapy is currently being studied in a phase II, open-label trial to evaluate valganciclovir (VGCV) as a treatment to prevent development of sensorineural hearing loss (SNHL) in infants with asymptomatic congenital cytomegalovirus (CMV) infection (NCT03301415) [7].

2.3 Natural History is Understood with a Recognizable Latent or Early Symptomatic Stage:

A natural history is readily apparent from the vantage point of SNHL. Lanzieri et al. (2018) compared the hearing trajectories among children with symptomatic and asymptomatic cCMV infection through 18 years. They reported that the severity of SNHL worsened with age for all case patients. Severity worsened for congenital/early-onset and delayed-onset SNHL and at all frequency-specific hearing thresholds. We analyzed hearing thresholds of the better- and poorer-hearing ears of 16 CMV infected patients with isolated congenital/early-onset or delayed-onset SNHL identified through hospital-based CMV screening of >30,000 newborns during 1982–1992 [19]. By 12 months of age, four of seven patients with congenital/early-onset SNHL developed worsening thresholds in the poorer-hearing ear, and one had an improvement in the better-hearing ear. By 18 years of age, all seven patients had worsening thresholds in the poorer- and three patients had worsening thresholds in the better-hearing ears. Hearing loss first worsened at a mean age of 2 and 6 years in the poorer-

and better-hearing ears, respectively. Nine patients were diagnosed with delayed-onset SNHL (mean age of 9 years vs. 12 years for the poorer- and better-hearing ears), six of whom had worsening thresholds in the poorer-hearing ear, and one in both ears.

2.4 There Should be a Suitable Test or Examination:

A number of suitable tests are available for cCMV diagnosis. Screening requires testing of saliva or urine via DNA detection of the virus through PCR or via a culture before the infant is 3 weeks of age. Later testing cannot distinguish congenital from postnatal infection, which does not cause SNHL. Saliva is easier to collect; however there is a risk for a false positive result presumably from breast milk [20, 21]. A prospective study of 20,000 newborns in Finland reported that 15 of 56 infants with CMV positive saliva (PCR), had a subsequent negative urine CMV PCR result [21]. Breast milk from seropositive mothers may account for these false readings. For that reason, we recommend waiting at least 90 minutes after breastfeeding to obtain a saliva sample and to obtain a confirmatory urine sample in those infants with a positive saliva result [16].

A child older than 3 weeks of age with a suspected congenital infection can potentially be diagnosed via CMV-DNA detection of archived neonatal dry blood spots, as samples are obtained for all newborns in the US. This scenario would be expected to occur most commonly in a child with idiopathic SNHL. This approach has several drawbacks, and many states do not keep these samples for more than a few months. Most children who pass the newborn hearing screen and later develop progressive and idiopathic SNHL would not be expected to present this early [22]. The other limitation involves the sensitivity of the assay. Multiple studies in the late 1990’s reported 100% sensitivity and specificity using this method of screening for congenital CMV [23, 24]. This high sensitivity is somewhat misleading however, as these studies did not determine the number of false negatives (infants with cCMV infection who tested negative on DBS PCR) [25]. Boppana et al (2010) reported on the sensitivity, specificity, and likelihood ratios of single-primer and 2-primer DBS real-time PCR assays for identifying infants with confirmed cCMV infection (rapid culture testing on saliva). cCMV infection was confirmed in 92 of 20,448 infants. Of the 11,422 infants screened using the single-primer DBS PCR, 17 of 60 (28%) had positive results with this assay. Among the 9026 infants screened using the 2-primer DBS PCR, 11 of 32 (34%) screened positive. They concluded that CMV testing with DBS real-time PCR had low sensitivity when compared with rapid culture of saliva, limiting its value as a screening test. There is an ongoing CDC funded study comparing saliva CMV PCR to DBS PCR [26]. Among the 9289 infants tested to date, 37 have been diagnosed with cCMV infection using saliva swabs. Of these 37, 28 were positive via DBS CMV PCR testing (76%; 95% CI: 60–95% CI, 6–28%). This study indicates a higher analytical sensitivity compared to the Boppana et al (2010) study and suggests that as more sensitive PCR methodologies emerge, DBS-based screening may become a viable, low-cost screening option.

2.5 Test Should be Acceptable to the Population:

Two studies indicate that the population is in favor of testing [27, 28]. Din et al (2011) first published a study to address this question. They analyzed responses to statements about CMV and newborn screening from 3922 participants in the 2009 HealthStyles survey, a

national mail survey designed to include a group similar to the US population. The majority of respondents strongly or somewhat agreed that they would want to have their newborn tested for CMV. These respondents agreed to newborn testing even with parameters such as: the tests lack of use in routine screening (84%), payment of 20$ (87%), or the possibility of CMV-related problems never developing (84%). Nearly half (47%) of them "would worry that the CMV test would lead to unneeded doctor visits and expenses," and 32% "think CMV problems are too rare to worry about." Surprisingly, the majority of respondents who had concerns (i.e. agreed that CMV problems are too rare to worry about or that they would worry about unneeded doctor visits and expenses) still agreed that they would want to know if their child had CMV even if he or she never developed symptoms, wanted to have their infant tested even if it was not part of routine screening with a specific doctor/hospital, and were willing to pay $20 to have their infant tested.

We surveyed three hundred sixty-five caregivers in Utah, whose children were seen in an Otolaryngology clinic at a tertiary pediatric hospital, about their knowledge and attitudes towards cCMV and cCMV screening [27]. The majority wanted to know if their child had cCMV (71.3%), even if the child was asymptomatic and were willing to pay $20 for cCMV screening (69.8%). Few parents (7.7%) were concerned about the stigma associated with a cCMV diagnosis when compared to the health concerns associated with cCMV, and few parents (13.6%) worried that cCMV screening would lead to unneeded doctor visits and expenses. Unfortunately, the majority of caregivers lacked an understanding of how cCMV was spread, could not name symptoms associated with congenital cCMV, and were unable to express why the idea of infant screening for cCMV was important. Most caregivers did not know that cCMV screening is required by law, if an infant fails their newborn hearing screening (NBHS) in Utah.

The reasons parents are in favor of screening are not clear. It would seem reasonable that parents would want to learn more about the health status of their children. From a community engagement approach of 13 parents whose children have cCMV infection, a general theme involved the desire for educational resources on this disease with possible research options for treatment [29]. From a survey of Utah parents seen in the Otolaryngology clinics, more knowledgeable parents were more likely to be in strong favor of cCMV screening [27].

2.6 Case Finding Should be Continuous (Not a "Once and For All" Project):

As described previously, the majority of cCMV infected children with congenital or late onset SNHL will develop progressive loss into adolescence [19, 30]. Thus, from the standpoint of hearing assessments, cCMV is not a "once and for all" condition. Given these findings, an informal International Congenital Cytomegalovirus Recommendations Group convened on April 19, 2015 as part of the 5th International Congenital Cytomegalovirus conference. The group reviewed and graded available evidence, and drafted recommendations that could be used to guide congenital cytomegalovirus diagnosis, prevention, and therapy [17]. They recommended to complete audiological testing at 6-month intervals during the first 3 years of life, and annually through adolescence (ages 10–19).

2.7 Accepted Treatment for Patients with Recognized Disease:

Treatment for a cCMV infection spans a wide range of options and includes: antiviral therapy, hearing amplification and/or cochlear implantation, speech and language and physical therapy. For CMV-induced hearing loss in particular, treatment with antiviral therapy has been attempted and continues to be studied for its impact on the amelioration of SNHL. Clinical trials reporting efficacy of antiviral therapy for CMV induced SNHL have included only symptomatically infected infants, but have generally found that antiviral therapy improves hearing outcomes for these children.[31, 32] Pasternak et al (2018) retrospectively presented their experience with the implementation of antiviral therapy in cCMV infected infants with isolated SNHL, who are otherwise asymptomatic. They reported that 68.6% of ears with a hearing deficit at baseline, improved in follow-up after the administration of antiviral therapy (either oral VGCV or ganciclovir). This study was not a randomized controlled trial, and based on the observation that cCMV-mediated SNHL can improve without therapy, it is impossible to determine whether the benefits reported can be attributed solely to antiviral treatment [33].

The National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group (CASG) group recently completed a randomized, double-blinded clinical trial primarily to determine whether the antiviral drug VGCV improves hearing and neurological outcomes in symptomatic and asymptomatic CMV-infected children with SNHL between 1 month and 4 years of age. Symptomatic CMV-infected children are not excluded from this study, which may prevent meaningful conclusions for asymptomatic CMV-infected children. Likewise, there is an ongoing observational study comparing the hearing outcomes of up to 40 asymptomatic infants with isolated SNHL in the Netherlands (CONCERT 2) treated with 6 weeks of VGCV and untreated controls that just finished enrollment [34]. We are currently conducting an international multi-center double-blind randomized placebo-controlled trial (ValEAR) to determine whether asymptomatic cCMV infected infants with isolated hearing loss have better hearing and language outcomes if they receive VGCV antiviral treatment (https://clinicaltrials.gov/ct2/show/NCT03107871). We will also determine the safety of antiviral VGCV therapy for these infants. This study will be unique in that the cohort enrolled will only include those with cCMV and isolated SNHL.

At this time, we do not recommend VGCV treatment for cCMV-infected children with isolated SNHL but ask that they are instead enrolled in one of the currently existing clinical trials. Two international consensus groups have stated that there is no definitive evidence concerning the potential benefit of antivirals for treatment of asymptomatic infants with isolated SNHL [17, 35] These groups currently recommend treatment only for severely symptomatic infants, particularly those with central nervous system involvement. Schornagel et al (2015) recommended caution in advising prolonged antiviral treatment in these children. David Kimberlin, the AAP Red Book Editor, warned: “With no proof of benefit and with the potential for harm from antiviral treatment, we should be very careful in considering universal treatment of these babies.”[36]

For infants and children who are deaf or hard of hearing, early intervention with speech therapy services, amplification and cochlear implantation are recommended [9, 37]. Since a HT-CMV approach will identify a number of cCMV-infected infants with and without

SNHL, this approach will facilitate prompt hearing loss diagnosis for at risk children and ongoing focused surveillance [3, 12]. Fowler and others have shown that cCMV positive infants are at risk for delayed onset, fluctuating and progressive SNHL [6, 22, 38, 39]. Repeated hearing testing of cCMV-infected children will also provide an opportunity to detect changes in hearing thresholds which would likely allow for earlier treatment [12]. There is a current lack of investigations evaluating the impact of treating cCMV-infected children with delayed onset SNHL with prompt auditory amplification and/or speech and language therapy. A broader compilation of evidence will be needed in order to draw more definite conclusions.

Implementation of a HT-CMV program could potentially improve and expedite diagnosis and treatment not only for cCMV-infected infants, but for all infants who fail their newborn hearing screen. In 2017, we showed an increase in the number of infants who achieved a timely diagnostic hearing evaluation once the HT-CMV screening protocol was implemented [12]. Delays in the diagnosis and treatment of hearing loss are a major challenge for universal newborn hearing screening programs. Shulman et al. (2010) surveyed 55 state and territorial UNHSI programs, and conducted site visits at 8 state programs and identified numerous issues in the follow-up of families with infants who did not pass their initial NBHS. Delay in diagnosis and treatment of hearing loss are major challenges for all universal newborn hearing screening programs and have adverse repercussions for speech and language development. Thus, HT-CMV screening has implications not only for those infected with cCMV, but for all infants who are hard of hearing.

2.8 Facilities for Diagnosis and Treatment are Available:

A major advantage of a HT-CMV screening program has to do with its link to an existing and successful universal newborn hearing screening program. In 1998, the federal Maternal and Child Health Bureau began requiring states to report the percent of newborns screened for hearing impairment before hospital discharge. This is one of the 18 core performance measures that states report annually to receive federal block grant funding [40]. By 2001, Early Hearing Detection and Intervention (EHDI) programs were established in all 50 states to address issues such as: appropriate medical, audiologic and educational intervention, coordination with the child's primary care provider, and successful tracking and surveillance [41]. In collaboration with state EHDI programs and representatives from other federal and advocacy agencies, the Centers for Disease Control (CDC) has developed and maintained national goals for these programs.

For the eighty-two birth hospitals participating in the ValEAR trial, we have been able to use these existing universal newborn hearing screening programs to provide the necessary facilities for cCMV diagnosis and treatment. Eighty-four percent of the hospitals actively track the number of cCMV infected infants identified, with the majority using their universal newborn hearing screening programs. Using a screening effectiveness score calculated as the proportion of cCMV positive infants over the number of infants who failed their newborn hearing screen, we found a statistically significant positive correlation between screening effectiveness score and those that actively tracked their cCMV identified infants[42].

2.9 Agreed Policy on Whom to Treat as Patients:

A Triological Society (TRIO) Best Practice paper was published in February 2018 to address the paucity of evidence-based reviews evaluating the role of CMV testing for infants who fail their newborn hearing screening [43]. Based on the current available evidence, the authors concluded that infants who fail their newborn hearing screening should undergo CMV testing. In November 2018, the American Academy of Pediatrics Leadership Forum passed a resolution advocating education on CMV testing [44]. The Academy recommended educating pediatricians, Early Hearing Loss Detection and Intervention (EHDI) coordinators, and others about the importance of timely testing for congenital cytomegalovirus infection (cCMV) when congenital hearing loss is suspected. They also advocated for the development of systems to assure completion of timely testing for cCMV infection. More recently, Shearer et al. (2019) presented a proposal for comprehensive newborn hearing screening to improve the identification of children with SNHL. This special article created on behalf of the Newborn Hearing Screening Working Group of the National Coordinating Center for the Regional Genetics Networks recommended targeted cCMV screening based on failed NBHS.

2.10 Costs of Case Finding (including diagnosis and treatment of patients diagnosed) Economically Balanced in Relation to Possible Expenditures on Medical Care as a Whole:

In addition to clinical demand and potential childhood health benefits, the cost effectiveness of these screening methods must also be considered. A study by Gantt et al. (2016) described the expected costs and outcomes of HT-cCMV screening. To identify one case of cCMV associated hearing loss, this study estimated costs at $975 by targeted screening. These estimates were calculated assuming screening costs between $10-$50 per newborn [45]. In Utah, HT-cCMV screening costs are estimated to be closer to $300 [43]. These studies describe a model that provides evidence for a net cost benefit in the use of a HT-cCMV approach in screening for cCMV. Of note, with the combined use of HT-cCMV screening and antiviral therapy, a previous study showed that the prevention of one cochlear implant, through the use of HT-cCMV screening, would pay for the cost of this approach in a statewide program such as the one in Utah[4].

3. Discussion

Based on our review using the Wilson and Jungner (1968) criteria, there is substantial rationale and evidence to support a hearing targeted approach to screen for congenital CMV. A formal position statement from the American Academy of Otolaryngology- Head and Neck Surgery, the American Speech-Language-Hearing Association and/or the American Academy of Pediatrics is needed. Ongoing clinical trials evaluating the efficacy of VGCV for asymptomatic or those with isolated SNHL will provide additional insight into therapy. Additional work regarding the efficacy of early identification and intervention of cCMV infected children with progressive SNHL needs to be completed. An investigation into diagnostic tests other than DBS CMV PCR testing are also needed to identify older children with late onset SNHL.

Although not included in the Wilson and Jungner (1968) criteria, one must also consider alternative approaches before implementing a HT-CMV screening program. Universal newborn cCMV screening – testing all infants for cCMV at birth – has been proposed as an alternative option. This approach would identify **all** cCMV infected newborns, including those infants who would develop hearing loss later in life. An estimated 64% of cCMV-infected hearing-impaired children could be missed with a HT-CMV approach [46]. A universal approach would require the screening of approximately 4 million newborns, an extremely labor-intensive undertaking. Concerns including: cost, the additional infrastructure for testing and tracking, and the resources to educate providers and families to deal with a positive diagnosis must be considered in the possible implementation of this program. Perhaps the Newborn Screening program at Ontario using DBS cards for universal cCMV screening that started July 2019 will provide insight into the challenges and advantages of this approach.

A hearing-targeted screening approach would involve between 52–76,000 newborns (1.4% −2% failure rate of NBHS) [47, 48], a more manageable population to screen. As mentioned previously, EHDI programs already provide the infrastructure for this approach. Components of any effective program need to include: cooperation and collaboration amongst providers (nursing, audiology, primary care, etc.), a process to ensure timely cCMV testing, effective tracking of patients and follow-up for parental counseling and support, additional workup as needed, and treatment.

A supplemental approach that may be used to improve detection of congenital CMV-infected infants involves a protocol that would initiate cCMV testing in infants who present with known **signs or symptoms** of this infection. Prior studies have reported poor detection in centers that lack a screening protocol for symptomatic cCMV-infected newborns [7]. The impact is problematic, as GCV and VGCV have been shown to improve hearing and neurocognitive outcomes in symptomatic newborns and are currently recommended for newborns with confirmed cCMV and the involvement of at least one end organ [11, 35]. Since 2016, this targeted approach has been implemented at two large birth hospitals and three neonatal intensive care units in Utah [49]. In addition to failed newborn hearing screening, infants with microcephaly, intrauterine growth restriction (IUGR), unexplained hepatosplenomegaly, transaminase elevation, petechial rash, persistent thrombocytopenia or intracranial abnormalities (e.g. calcifications, polymicrogyria) undergo screening for cCMV. Out of the 754 patients who underwent screening, 21 tested positive for cCMV (2.8%). At this point in time, the results indicate that 12 symptomatic infants were diagnosed with cCMV, and without this program, may not have been diagnosed appropriately. Implementation of this expanded targeted cCMV testing approach for symptomatic infants is currently being implemented at all University and Intermountain hospitals in Utah and Idaho. Parkland Hospital in Dallas, Texas follows a similar approach, completing CMV testing in clinically symptomatic infants, those who do not pass newborn hearing screening (HT-CMV screening) and infants who are born to HIV positive mothers[3, 50]. In a 5 year review of this protocol (conducted in 2010), 50 infants were identified with congenital CMV. Of these, 22 were identified due to clinical signs (symptomatic), 19 due to failed newborn

hearing screening and 9 due to maternal HIV infection[50]. Future studies will be needed to determine the true impact of this approach.

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Recommended Clinical Practice:

Currently over 100 birth hospitals have implemented hearing targeted cCMV screening programs as part of their standard of care. Based on our review using the Wilson and Jungner (1968) criteria, there is substantial rationale and evidence to support a hearing targeted approach to screen for congenital CMV. For these reasons, we recommend that newborns who fail their newborn hearing screen should undergo cCMV screening.