Drug Development for the Treatment of Congenital Cytomegalovirus Infection and Neonatal Enterovirus Infection - Day 2

Moderated by Aimee Hodowanec, M.D.

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Reported by: Alexandra Hobrecht

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APPEARANCES

List of Attendees:

Mark Abzug, M.D. (by videoconference)
Tien Bo, Pharm.D. (by videoconference)
John Concato, M.D., M.S., M.P.H. (by videoconference)
Lindsay DeVries, Au.D., Ph.D. (by videoconference)
Roberta L. DeBiasi, M.D., M.S. (by videoconference)
Rachel G. Greenberg, M.D., M.B., M.H.S. (by videoconference)
Paul Griffiths, M.D., D.Sc. (by videoconference)
David W. Kimberlin, M.D. (by videoconference)
Tatiana Lanzieri, M.D., M.P.H. (by videoconference)
Aimee Hodowanec, M.D. (by videoconference)
Ryan Kau, M.D. (by videoconference)
An N. Massaro, M.D. (by videoconference)
Emma Mohr, M.D., Ph.D. (by videoconference)
Lily (Yeruk) Mulugeta, Pharm.D. (by videoconference)
Megan Honor Pesch, M.D., M.S. (by videoconference)
Natalie Pica, M.D., Ph.D. (by videoconference)
Mark R. Schleiss, M.D. (by videoconference)
Kunyi Wu, Pharm.D. (by videoconference)
Prabha Viswanathan, M.D. (by videoconference)

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APPEARANCES (Cont'd)

Betsy Pilon, Executive Director (by videoconference)
Corey Farley, AV Staff (by videoconference)
Marcus Washington, AV Staff (by videoconference)

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PROCEEDINGS

DR. HODOWANEC: All right. Good morning. And welcome to Day 2 of our workshop: Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital CMV Infection. Thank you, all for joining us. Next.

We had a very productive Day 1 yesterday. In the morning, we heard about the general principles of pediatric and neonatal drug development, as well as an epidemiologic, virologic, and clinical overview of enterovirus infection in neonates.

Then in the afternoon, we had a robust panel discussion regarding the many enterovirus drug development challenges. Key knowledge gaps were identified, and potential solutions to some of these challenges were proposed.

We have another ambitious agenda for today. This morning, we will have epidemiologic and clinical overviews of congenital CMV infection, as well as several presentations regarding congenital CMV drug development.

These morning sessions will serve to

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set the stage for congenital CMV drug development panel discussions in the afternoon. Next, please.

Before I turn the mic over to our first speaker of the day, I would like to reiterate some important housekeeping items.

As noted yesterday, this meeting is being recorded. Speaker slides, transcripts, and recordings will be available on the meeting's webpage in the coming weeks.

Speaker and panelist affiliations and voluntary disclosures are already available on the meeting's webpage under meeting materials. Note that this is the same webpage that you visited to register for the meeting.

For all members of the general audience, your microphone and video camera are automatically turned off.

Should you have any questions or comments, please submit them using the Q&A feature at the bottom center of your Zoom screen. We may not be able to respond to all questions and comments.

Lastly, if you're experiencing any

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technical difficulties, please contact one of our outstanding AV staff, Corey Farley or Marcus Washington. Next slide, please.

And we will now begin Session 1. During -- during this session, our presenters will provide epidemiologic and clinical background information regarding congenital CMV infection. We will also have the opportunity to hear parent perspectives on congenital CMV infection.

We are thrilled to have Doctors Tatiana Lanzieri, Mark Schleiss, Roberta DeBiasi, and Megan Pesch here with us for this session. Next slide, please.

So without further ado, I'd like to introduce our first speaker, Dr. Tatiana Lanzieri, the CMV Program Lead of the Measles, Rubella, and CMV Epidemiology Team at the Centers for Disease Control and Prevention.

Dr. Lanzieri's talk is entitled "Surveillance in Epidemiology of Congenital CMV in the United States."

Thank you, Dr. Lanzieri.

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DR. LANZIERI: Thank you, so much. It's a pleasure to be here, and thanks for the opportunity to speak with you today.

Just one correction. I'm just the lead for the CMV Program. Measles and Rubella and CMV Team are under the leadership of David Sugarman.

And to start, I have no conflict of interest, and the findings and the conclusions presented here do not represent the official position of CDC. Next, please.

So many of you know this slide, based on estimates from newborn screening studies. Congenital CMV infection occurs in an estimate 4.5 per 1,000 live births in the U.S., which corresponds to about 16,000 infected newborns just in 2020.

As shown in the left-hand side, about 10 percent of infected babies are symptomatic at birth. And off-label use of antivirals have been recommended for this group in the U.S. for over a decade.

Fifty to seventy percent of these babies will have neurological impairment. And most

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infants, 90 percent, are asymptomatic at birth. Ten to fifteen percent of them will have isolated sensorineural hearing loss that is congenital or has a late onset.

The use of antivirals outside research studies has not been recommended for this group. But it is evolving. The recommendations are evolving.

Of all infants with CCMV, 75 to 80 percent have no long-term health problems, and this generates a lot of debate around universal newborn screening for CCMV, including concerns for overtreatment. And next, please.

In the U.S.'s studies, 5 to 10 percent of hearing loss in children ages 2 years or less are attributable to CCMV. Sensorineural hearing loss occurs in about 50 percent of infants who are symptomatic at birth and 10 to 15 percent of the asymptomatic ones, as I said before.

Prior to newborn hearing screening, these babies that appear well in the newborn exam and go on to later develop hearing loss, they were considered asymptomatic. So I'll not talk about --

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too much about asymptomatic. I will treat them as isolated hearing loss.

Importantly, up to half of the cases of CCMV-related sensorineural hearing loss in either symptomatic or isolated hearing loss may not be detected by newborn hearing screening. Next, please.

A few additional points to highlight for children with CCMV and isolated hearing loss: The hearing loss is typically progressive, does require close audiology monitoring for early intervention; two, children with -- who initially have unilateral hearing loss have a higher risk of developing bilateral loss.

As shown in the survival curve on the right, a higher proportion of infants with unilateral congenital loss in red developed hearing loss in the contralateral ear, as compared with infants with bilateral normal hearing at birth in blue.

By age 2 years, three in five of the children with CCMV and isolated hearing loss will have profound hearing loss, unilateral or bilateral, and may become candidates for cochlear implants. Next.

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So I'm going to give a brief little update on the status of newborn screening and surveillance for CCMV in the United States. Next.

In 2013, Utah began hearing targeted screening, which means infants who failed their newborn hearing screening are referred for CMV testing.

Several states and hospital networks have followed with this strategy. And currently, Utah also performs expanded targeted early testing for CMV among infants who present with certain clinical signs that lead to suspicion of CMV, but were -- earlier not -- not all of -- all of them were tested.

In 2023, Minnesota was the first state to implement universal screening for CCMV, and we will hear more about that in the next presentation.

And in addition, New York State is conducting a pilot, and legislation has been approved in Connecticut, pending implementation, and New Jersey, pending inclusion in the recommended universal screening panel, or RUSP, which CMV is not part of. Next.

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Regarding surveillance, CCMV is not a nationally notifiable condition. The standardized case definitions for CCMV infection and disease were approved in 2023.

And currently, at least 12 states have initiated surveillance efforts to monitor trends in disease prevalence, connect families to resources and services, and track compliance to hearing targeted screening.

Case ascertainment methods and data collection vary. For case ascertainment, some states rely on administrative data or clinical reports. Others will include laboratory reporting.

Few states collect data on long-term outcomes. Thus, incomplete case ascertainment and limited data on long-term outcomes contributes to limited information on disease burden. Next.

At CDC, congenital CMV was recently added to the SET-NET and MAT-LINK. These are surveillance systems to identify the impact of emerging health threats on pregnant people and their infants.

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Five jurisdictions participate in the CCMV SET-NET project in the first year, Minnesota, Utah, New York, New Jersey, and Iowa, and two others, Virginia, and Illinois, were added in the second year.

More academic sites are participating in the CCMV surveillance module in MAT-LINK. And the initial goals of the surveillance projects are to identify and evaluate methods for CCMV surveillance and assess the visibility of longitudinal data collection for infants with CCMV through the age of 3 years. Next.

The ultimate goals of CCMV surveillance are to inform clinical guidance, vaccination, and newborn screening policy.

We are on the building phase, and our aim is to use surveillance data to monitor trends in disease and identify groups at higher risk of CCMV, characterize the clinical spectrum of disease, long-term outcomes, and access to services, as well as monitor trends in the use of antivirals, including acuity and whether it is in line with recommendations, as well as assess real-world effectiveness. Next.

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So while our surveillance data are in the works, I want to share some findings from analysis of administrative data. Next.

This graph shows a slight increase over time in the administrative prevalence of CCMV disease, defined as the presence of CMV diagnostic codes within four to five days of life.

This scale is for 10,000, so infant diagnoses are in order of magnitude of the estimated prevalence, which as I said in the beginning was 4.5 per 1,000 live births. Next.

Before I show data on antiviral use, I'd like to revisit treatment recommendations for various groups.

Currently, as per AAP Red Book, treatment is recommended for infants with moderately to severely symptomatic CCMV disease who exhibit multiple signs or -- or central nervous system involvement.

That consists of six months of oral valganciclovir starting within the first month of life. Intravenous ganciclovir may be used initially

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for those who are unable to take oral medication.

For infants with isolated hearing loss, there is no formal recommendation for antiviral therapy in the U.S.

Recommendations in Europe are evolving. These infants have been considered by the European Consensus Group to have CNS disease, central nervous system disease, hence, a treatment recommendation, and more recently, a six-week therapy has been recommended, based on findings of the CONCERT study in the Netherlands. However, limited data on long-term efficacy exist. Next.

We used electronic health records to assess use of ganciclovir and valganciclovir among infants with CCMV.

And as you can see in the first row, 4 percent of infants with CCMV had ganciclovir prescriptions starting at a median 13 days for a median duration of 8 days.

Thirty-three percent had valganciclovir, and twelve percent had both antivirals prescribed. The start of valganciclovir was a bit

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delayed at a median 45 days, and median duration was little -- a little less than 6 months.

Half of infants with CCMV were not prescribed antivirals. Neutropenia, in the last column, was more common in treated infants. Next.

We have seen the use of antiviral therapy for infants with CCMV disease increased from 2009 to 2019, and the reason for the dip in the 2019 data for commercially insured infants is unclear. Next.

When we look at the proportion treated by CCMV disease category or disease severity category, the degree of change is similar for infants with either moderate to severely symptomatic CCMV disease in line with recommendations and for infants with isolated hearing loss, despite not being recommended in the U.S. Next.

In summary, today I gave a brief overview of the dynamic landscape of U.S. newborn screening, surveillance, and treatment recommendations for CCMV. This momentum would likely increase identification of infants with CCMV infection.

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And we have seen an increasing trend in use of antivirals since 2010, mostly in line with prior recommendations, but also for infants with isolated hearing loss.

This highlights the need for increasing provider education and shared clinical decision making, given limited data on long-term efficacy of antivirals, as well as the need for assessing real-world effectiveness of antivirals recommended off-label and for developing new drugs.

And I look forward for the discussions today. Next. My acknowledgements to all who contributed to this presentation, and thank you, so much.

DR. HODOWANEC: Thank you, very much, Dr. Lanzieri, and my apologies for the oversight regarding your affiliations.

Next, I'd like to introduce Dr. Mark Schleiss, an American Legion and Auxiliary Heart Foundation Research Professor in the Department of Pediatrics at the University of Minnesota Medical School.

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Dr. Schleiss' presentation is entitled "CMV and the Maternal-Fetal Dyad: Whom to Screen, How to Screen, and When to Treat?" Thank you.

DR. SCHLEISS: Thanks. Thanks, so much. I appreciate the opportunity to be here. I'll just -- up front, I'll just say I don't have answers to any of these questions in the title.

But the next slide gets us started, anyway, and gives an overview of the problem with maternal screening, which is that we don't really have any recommendations in the United States from ACOG, a maternal antibody screening.

This is really, largely a reflection of the fact that CMV's sort of prevalence is high among women of childbearing age and moreover that reinfections with transmission that can lead to symptomatic disease can occur in seropositive women. So this is a big challenge.

Having said that, there are a lot of studies that have looked at combinations of IgG, IgM, and avidity index sero-screening. Dr. DeBiasi is going to talk about that a little bit.

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And based on sero-screening and amniocentesis, there is some information about the use of high-dose valacyclovir that I'll come back to in a moment.

In the next slide, I think we have the most recent guideline that I could find from the Society of Obstetrics and Gynecologists of Canada. And -- and it's interesting to reflect on this. Again, ACOG has not taken any formal position on this. Although, it's under discussion.

But in provinces in Canada where IgG avidity testing is available, screening for primary CMV infection in the first trimester can be offered, especially in women who are at high risk, particularly women who have toddlers and young children.

And so this has become a much discussed topic in many centers in the United States. And now that we have universal newborn screening in Ontario and Saskatchewan with other provinces on the way in Canada, it will be interesting to see how these recommendations evolve.

The next slide summarizes the statement

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about prenatal treatment with valganciclovir. And this study talks about or reviews a double-blind randomized control trial on 90 -- 90 pregnant patients with primary CMV infection acquired in the first trimester.

And this was the paper in Lancet, now published a couple of years ago from the group in Israel, Shahar-Nissan, et al.

They found that individuals who had primary -- serologic evidence of primary CMV infection did have some improvement in a positive amniocentesis.

It was significantly less likely in the valacyclovir group, only 2 out of 19 amniocenteses in that study, compared to the placebo group, which was 11 out of 48 -- excuse me, 11 out of 23 amniocenteses.

And an important caveat there is that this was a study of a fetal infection, not a congenital CMV. The benefit was limited to those with first-trimester infections. The next slide goes into a more recent paper that looked not only at amniocenteses, but true congenital CMV infection.

And so interestingly, in this more

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recent study with the reference provided below, there was an effect of valganciclovir on the rate of congenital CMV diagnosis at the time of amniocentesis, but not at birth.

And so this is an area that needs to be further studied and discussed. The next slide now shifts into what about newborn screening, and newborn screening for CMV -- congenital CMV, has largely fallen into these categories so called targeted screening or hearing targeted screening or universal screening.

The next slide summarizes important data from Karen Fowler and others about asymptomatic congenital CMV and infants with hearing screen findings.

And the next slide from the CHIME study shows that in Karen's study, there -- there was a significant proportion of kids who had passed their newborn hearing screen, but went on to have sensorineural hearing loss.

And so I think this is the -- the central core of the issue with targeted screening is

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that we'll miss a substantial proportion of children who go on to have sensorineural hearing loss, which as we've heard is the -- the main driving force, I believe, behind CMV screening to capture those children and offer early identification and intervention.

The next slide summarizes the pros and cons of whether or not universal congenital CMV screening should be provided as a part of the recommended uniform screening panel or RUSP.

And as -- as many in the audience know, there have been petitions to the committee on -- advisory committee, on newborn screening, which have not really been vetted yet because of concerns that universal congenital CMV screening doesn't fit the classic paradigm for universal screening tests.

Those who are proponents of universal screening point out the delay in hearing loss, the progressive nature, the option of antiviral therapy.

But as Dr. Lanzieri pointed out, most infants are asymptomatic. And we do have, I think, a real issue with overuse of antivirals, not to mention

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the generation of perhaps unnecessary parental anxiety for screen-positive babies who actually have a good prognosis for a normal outcome.

The next slide gets into some of the details on the advisory committee on inheritable disorders in newborns and children. This was a petition or a letter offered a couple of years ago now.

Megan Pesch, who is on this call and will have a presentation later, was the driver behind approaching the committee.

And the Nomination and Prioritization Workgroup concluded that there was insufficient information to move the nomination forward for universal congenital CMV screening, and these were the five criteria that they outlined in their response letter. It's available online.

And they wanted to see more data from a pilot study, a cleaner case definition, very importantly, sensitivity of a screening test that would be used, and not to mention the clinical utility of those babies who would be identified and what the

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treatment options might be. All areas of controversy.

The next slide then moves into the issue of what do we use for universal congenital CMV screening.

And the landmark CHIMES studies of the early 2000s demonstrated the dried-blood-spot PCR, which obviously has a lot of appeal, because it's collected on newborns, had a suboptimal sensitivity in that perspective study, where saliva PCR had a very high sensitivity.

So most of the discussions in recent years have been focused on saliva-based PCR.

The next slide gets into some work that I commenced seven or eight years ago now, chiefly in collaboration with Sheila Dollard at the CDC and colleagues at the Minnesota Department of Health.

And here's a paper from Sheila's lab that looked very carefully at extraction techniques and methodologies.

And with improvement in extraction techniques, chiefly an improvement over the magnetic bead-based DNA recovery scheme or profile that was

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used for the CHIMES study, we decided to take another look at dried-blood-spot PCR.

The rationale being that perhaps we would see an improved sensitivity to -- in comparison to the CHIMES study.

The next slide shows what we pursued, which was a study in six newborn nurseries in the Greater Twin Cities area.

In the upper left, you see a lonely red arrow up there in St. Cloud, Minnesota, which is a little bit more of a rural area, and we looked at newborns in the -- chiefly in the normal newborn nursery and obtained consent to swab their mouths for dried-saliva PCR and to get some hunches from the health department to look for CMV DNA.

The next slide shows some of the laboratory approaches. I won't belabor the points. I'll just say that my lab used a UL 83 based real-time PCR detection assay that we had been developing for quite a number of years. The CDC lab used an IE 1 primer set. And in my lab, we also did the saliva PCR for comparison.

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The next slide shows the data results that we took action on. Any baby that was screen-positive, we used the Rawlinson, et al., criteria.

First of all, confirmed the diagnosis with the urine CMV PCR, so we -- we didn't define a child as having congenital CMV unless they had a confirmatory urine sample.

And then we obtained an audiologic assessment, biochemical markers, ophthalmologic, and had ultrasonography studies, and then defined one of these four disease categories from the Rawlinson criteria.

The next slide shows the actual symptom categories, again, from Rawlinson, et al., and this is an area that, as Tatiana alluded to, is also under discussion in terms of which babies we end up treating with antivirals.

Next slide shows the sensitivity and specificity. This was an interim analysis. The final analysis shows similar numbers.

In the University of Minnesota lab, in the CDC lab, using different primer sets, sensitivity

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of the dried-blood-spot PCR, analytic sensitivity in the mid-70 percent range, we had some positives that were negative in CDC and vice versa, so when we combined the results, it got up in the -- in the 85 percent range for sensitivity.

The next slide shows the viral load distributions in confirmed cases, and I just include this slide to point out that we only have one false positive in the dried-blood spot.

But a number of a false positives is shown in red on the left side in saliva -- interestingly, a lot of very low saliva viral loads in babies who did have confirmed congenital CMV.

So it remains unclear whether a cut-off in viral load and saliva PCR can be a defining factor in deciding which babies need further workup and confirmation.

The next slide shows the overview from the study. In total, we ended up consenting just over 24,000 families and had 87 cases of confirmed congenital CMV. So for an overall prevalence of somewhere between three and four per thousand.

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The next slide has the sensitivity and specificity for the final numbers from the study, and the next slide has a summary of how these babies fell out categorically.

And so 68 out of the 87 infants were classified as asymptomatic by the Rawlinson criteria. Although, two of those babies did go on to have late onset sensorineural hearing loss, and we're still following them, and I anticipate there may be additional babies, because we know hearing loss can be delayed.

In total, 11.5 percent have had some degree of hearing loss in -- in the follow-up to date, and 15 infants fell into a symptomatic category with either mild symptoms or moderate to severe symptoms.

The next slide shows the clinical sensitivity. So in addition to the analytic sensitivity, we wanted to take a look at whether a positive screening test identified a baby who went on to have some sort of CMV-related problem.

And for this definition, I lumped together both, babies who had the late onset hearing

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loss, as well as mild or moderate symptoms, and the clinical sensitivity of the DBS was more robust than the analytic sensitivity.

So an argument can be made the dried-blood-spot testing will actually identify those babies who go on to have problems.

We were judicious in the babies that we offered treatment to, and most -- for the most part, only symptomatic babies were treated with valganciclovir.

I did have one family in a completely asymptomatic category that did want treatment. And so in a shared decision-making sort of model, we -- we did treat that infant. But for the most part, we -- we are very judicious in antivirals in this pilot study.

The next slide shows the summary to date the for where we stand with antivirals, and we've heard a little bit about the recent study -- the CONCERT study, from the Netherlands.

We had a plenary session at PAS just a couple of days ago in which Mary Caserta presented the

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current Red Book recommendations for antiviral therapy.

And as many of you are aware, those are being modified now, such that we can commence the treatment of infants within 13 weeks of birth for babies who have moderate to severe symptomatic disease, including those who have CNS involvement.

The recommendation is still for six months of oral valganciclovir. But based on the CONCERT study, the Red Book Committee, and the current AAP statement, makes the statement that we can offer six weeks of oral valganciclovir to those babies.

And -- and so this will be an area of considerable discussion hopefully during the workshop this morning and as time goes by. It is, I think, important that we can commence therapy out to 13 weeks of age now.

And it's been my impression that many families feel tremendous pressure and stress that they're racing the clock to complete this diagnostic workup by 1 month of age, which often is very difficult to get referrals to audiologists and

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ophthalmologists and obtain neuro imaging studies.

And so I think having a little buffer of extra time is actually very important for these families.

Next slide summarizes where we got with universal screening in Minnesota. This was actually one of my patients, little Vivian Henrikson.

I was talking with her mom in clinic in 2016, and we were certainly talking all the time about the various state initiatives to codify a targeted screening, and we thought, well, why don't we go down to the state capital and see if we can capture some attention.

And it only took us six years to get a bill through the Minnesota Legislature. But we found some legislative partners who signed on.

One thing that was extremely important was negotiating the fiscal note with the legislation, and the state budget surpluses that occurred in -- in the immediate aftermath of COVID really were very helpful. And we put together broad coalition. We got a lot of public attention, a lot of media events, a

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lot of get-togethers of families.

And the next slide shows some really landmark work done by another parent advocate, Stephanie Steidl, and this is her child, Hank, who actually was identified in our universal screening pilot study and appeared to be asymptomatic at birth and went on to have delayed onset CMV retinitis -- kind of an usual case in its own right.

But be that as it may, the next slide shows the announcement just over a year ago now of initiation of universal screening. Folks in my lab group that were working on this, including Claudia Fernandez and, you know, Mary Hernandez, and Mark Blackstad. And here's Vivian all grown up now with her brother and her mom.

And so in the spring of 2023, we began universal dried-blood-spot screening in Minnesota for congenital CMV.

The next slide shows where different states are with this. We have legislation in Connecticut, shown in green. As was alluded to, New York is currently doing universal screening as well,

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but under the aegis of a NIH-funded program. Although, they seem to show every sign of incorporating that into clinical practice at the end of that pilot study.

And then two provinces in Canada, Ontario and Saskatchewan, are doing universal congenital CMV screening. Although, interestingly, not under the aegis of the newborn screening programs, but in Ontario under the aegis of EHDI, Early Hearing Detection and Intervention.

And that's, I think, an area for discussion too; where does universal CMV screening belong; does it belong in -- in newborn screening, or does it belong in -- in EHDI? And that will be a topic for future discussion as well.

The next slide shows exciting development by the American Academy of Otolaryngology and Head and Neck Surgery, who endorsed universal congenital CMV screening just a couple of months ago.

We have not seen any endorsement from other professional medical organizations in the United States. Although, I think this too will be an area of

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discussion in the years ago.
Next slide then is where we stand with future uncertainties. Apologies. Hold on.
I think that's my cue that I'm just about done. But these are some of the imaging findings that we struggle with: subependymal cysts, leukostriate [sic] vasculopathy, does every baby need an ophthalmologic evaluation, and as Tatiana alluded to, uncertainties about antiviral treatment.
My last slide, thankfully, is an acknowledgement slide. And I want to acknowledge Sheila Dollard and Tatiana Lanzieri at the CDC, Sandra Rosenthal at MDH, who has been a key partner in this, and then at the University of Minnesota, in particular, Erin Osterholm, who's been my partner in the CMV follow-up work, and then members of my lab group as shown here.
Thank you. And I'm sorry about the dogs.
DR. HODOWANEC: Thank you, very much, Dr. Schleiss for that wonderful presentation, and thank you for sharing all the important work that

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you've been involved in, in Minnesota.
I am happy to now introduce Dr. Roberta DeBiassi, chief of the Division of Pediatric Infectious Diseases and Robert H. Parrott Professor of Pediatric Research at Children's National Hospital and Research Institute.
Dr. DeBiasi will present "New Horizons in Clinical Diagnosis and Treatment of Congenital CMV Infection." Thank you, Dr. DeBiasi.
DR. DEBIASI: Thank you, so much, for the introduction and opportunity to participate in this meeting.
And I have to say, Dr. Kimberlin and Dr. Abzug were who introduced me to the whole world of congenital CMV back when I was fellow, and I have to point out that two of the organizers of this workshop were fellows at Children's National long ago. So it's -- it's amazing how things have progressed over time.
Next slide, please. So the objectives are to briefly review the physical exam, lab, radiographic features of infection, congenital CMV

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infection, review diagnostics both pre- and post-natal, discuss features of symptomatic congenital CMV infection in a little more detail, discuss prenatal and postnatal treatments, and then a brief overview -- literally, one slide that just shows the many areas that are being looked at to focus on screening, prevention, diagnosis, and treatment.
Next slide. So I don't think we need to belabor this. But I just want to point out again, like all the other speakers have, the real crux of making these decisions about who to study, who to treat, is this conundrum that it's the -- the minority of infants that are symptomatic at birth that have the biggest sequalae and then a large number of children who are asymptomatic, but still can have hearing loss or developmental delays as they progress through their life.
Next slide. And it's really these decisions that are difficult for families and doctors to talk about together when making the decisions about treatment. Next.
So for clinical manifestations at --

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you know, at a big medical center, we get referrals from a variety of ways. They may come through the prenatal pediatrics program, through maternal fetal medicine physicians that have found abnormalities on exam. They may come from the NICU in a baby who is transported. They may come from a nursery -- for a liveborn nursery.
And I think when we think about designing these studies going forward, the way these children will present clinically are also different.
So this is just on one slide, a summary of many of the prenatal findings that can be suggestive of congenital CMV infection and lead to referrals to our program.
In the brain, there can be calcifications, ventriculomegaly, or microcephaly, pseudocysts in various areas, polymicrogyria, cerebellar hypoplasia.
In the GI system, we often see hypoechogenic fetal bowel, ascites, hepatosplenomegaly, or calcifications within the liver.

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We can see fetal growth restriction, pleural or pericardial effusion, amniotic fluid abnormalities, hydrops, and then, importantly, placental abnormalities, which, of course, is not specific to CMV.

When we see these findings and they're referred to our congenital infection program, we offer prenatal follow-up consisting of serial ultrasound every two to four weeks to see how these abnormalities progress.

And it's of note that these abnormalities can appear even up to three months after a mother is initially referred due to a primary infection. So you can't really clear the baby prenatally, even for a significant period of time.

Fetal MRI can diagnose CNS findings not seen by ultrasound and at some centers is readily available and certainly can be used on a research basis, as we've done in some other countries.

Next slide, please. So postnatal clinical manifestations I think most people are familiar with -- small for gestational age infants,

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specifically those that are asymmetric, meaning the head is small, whereas the rest of the body is not, jaundice, which is usually a direct hyperbilirubinemia and can be more prolonged than the physiologic indirect hyperbilirubinemia of the newborn.

The blueberry muffin rash, which is shown here, which is raised, palpable, and actually represents extra medullary hematopoiesis as a reaction to the suppression of the cell line due to CMV or just frank petechiae or purpura separate from the blueberry muffin rash.

And then shown on the right is hepatosplenomegaly in an infant. Next. So CNS infection, of course, is the most concerning and what we are trying to prevent, if possible, or ameliorate if present.

And if CMV enters the CNS early in development, this is when the most significant structural damage to the brain can ensue.

It's really unclear why fetal newborn brains are more susceptible to CMV compared to the adult brain. But obviously, the developing cells that

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are infected are susceptible to actual cell death by lysis or apoptosis.

And the structural abnormalities really depend on when in the gestational age of the fetus that this infection of the neurons occurs.

The pathogenic spectrum of -- or the result of that infection, as I said, can be lytic infection of the neuronal progenitor cells, or there can be vasculitis, which results in loss of the supporting vessels and blood flow to the developing brain, or frank meningoencephalitis due to release of inflammatory mediators.

And the calcifications that we often see -- and you'll see on the next couple of slides, are from extravasation of blood from damaged microvasculature.

Next. So there are ocular manifestations of CMV, which are considered CNS disease. This is the typical chorioretinitis that you can see here, and we can also see cataracts in children. Next.

And then these are some images of the

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typical periventricular calcifications that are best seen on ultrasound, less seen on MRI. But as I said, MRI picks up some of the structural abnormalities differently.

So at our center, we like to use both. And we can talk about that in the discussion period about the feasibility and some protocols to do that without anesthesia under 2 months of age.

Children can also present with just lethargy, poor suck, or hypotonia as a manifestation of CNS disease.

We also can see periventricular cysts of ependymal pseudocysts or white-matter abnormalities, as well as atrophy or migrational disorders, the most concerning of which is polymicrogyria, in which the neurons do not migrate as they are developing in a normal way and lead to abnormal gyral patterns. Next slide.

So this is a autopsy photo that -- that demonstrates both microcephalic, as well as abnormal gyral pattern where you don't see the gyri; it's disorganized, and it's smooth.

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And this occurs in -- if the infection occurs during the most critical period in the third to eight week -- third to eighth week of gestation.

But CMV infection, even in the later trimesters, although it will not lead to polymicrogyria, can still lead to CNS problems, including the problems within cephalitis and microvasculature that we mentioned. Next.

And this is just another autopsy photo to demonstrate. Around the large ventricles, you can see the white periventricular calcifications, the dilated ventricles, and the atrophic cortex, so very thin cortex, very big ventricles. Next.

So hearing loss you've heard so much about. I don't think we need to belabor this, because I think prior speakers have given a lot of detail.

But the bottom line is that pathogenesis is still poorly understood. There are certainly direct effects. But there are also animal models and "fetopsy" studies that suggest that inflammation, as a result of the infection, may be equally or more important in the development of the

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progressive or late onset hearing loss.

And therefore, when we talk about treatments that really currently target viral replication, some centers have proposed targeting post-inflammatory response or a combination thereof. Next.

So diagnosis. Next. Prenatally, as was alluded to, ideally, we would know the serostatus of every woman prior to pregnancy. But that's just not the case in the U.S.

I think all of us who have taken care of these babies -- it's heartbreaking when a mom tells us, "I didn't even know that CMV existed. Why didn't someone even tell me this and give me the option of knowing?"

So that's another area of discussion for legislation and has been adopted in some states about education, even if nothing else is done with screening.

But if the CMV IgG and IgM on the mother are both negative, that identifies a seronegative mother, who is at risk, particularly

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someone who has a toddler at home, as was mentioned, since children in daycare can be excreting CMV almost all the time. If you go into a daycare center, probably 75 percent of those children are -- are excreting CMV.

If the CMV IgG and IgM are both positive, this could represent either primary infection or reactivated disease.

I don't have a pointer. But you can see in the slide that there's a little gray bump at the earlier time period on the X axis, and then a little gray bump on the X axis further out.

And so if you have that IgM, one way to distinguish if this is an early infection or reactivated disease is to use the avidity index of the IgG in which the avidity low suggests that this is a primary infection, whereas if this is a now mature and highly avid antibody for IgG, you're likely in that second reactivated hump to explain the IgM.

But it also was pointed out, it's not completely reassuring, even if you have a reactivated disease, because that's a large number of women, and

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there still can be transmission to the infant.

If only the IgG is positive and the IgM is negative, it's likely this is a prior infection. But I must say, if it's obtained for the first time from a pregnant mother who has symptoms, you still may wish to do avidity.

And we have had women, just because of timing issues, where they had lost their IgM. But it really was a primary infection that was picked up by the avidity testing. Next.

Amniotic fluid PCR is another area that had been looked at most -- most, I guess, intensively by Lazzarotto's group. And the idea here is that it's very sensitive and specific, but it has to be done at a certain time after symptom onset and gestational age.

And the real research question is, are there thresholds CMV viral is predictive of symptomatic disease? There really have been conflicting results on this.

Lazzarotto's data showed that over a thousand copies was highly predictive that the fetus

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would be infected, over ten to the fifth was predictive of symptomatic infection, and less than 500 cutoff was unlikely symptomatic.

But there's a gap in between, and -- and other groups have not really found these clear cutoffs, so it's unlikely how useful this will be. Next.

Postnatal diagnosis has been talked about in the prior speakers. We really have to diagnose this in the first three weeks of life, because the CMV is so prevalent out in the community, and infants can be infected with CMV postnatally for other reasons.

So really, to be secure with the diagnosis in an asymptomatic child, you need to have the testing in the first three weeks of life and, therefore, getting the urine or saliva PCR or going to the health department to get the neonatal blood spot is really the ways that we -- we do this.

I mentioned that neonatal blood spot has lower sensitivity. But as you've heard, there is some exciting data that perhaps the sensitivity may be

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higher.

I will say, depending on your state, it may be easier or harder to get the blood spot. For instance, in Virginia, they actually hand the blood spot -- you know, one blood spot to the family when they leave the nursery so that they have direct access to their blood spot for whatever reason, whereas in some other jurisdictions, it's nearly impossible to get it, or they discard them in a very short period of time.

Serology has less of a role postnatally because of the maternal transfer of IgG to the infant and the unreliability of IgM testing.

Next are postnatal evaluations to identify symptomatic congenital CMV if you have the infant in front of you and you're doing the consult or -- or you're in your office and -- and wondering if this child might have a symptomatic disease.

Very close attention to growth parameters, particularly non-symmetric SGA, careful physical exam of the liver, spleen, skin, and eyes, as we mention for the reasons I showed you on the

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photographs.

A CBC with differential to identify anemia from a cytopenia, a liver panel to look at ALT total and direct bilirubin, head ultrasound, and depending on your center and accessibility, MRI without anesthesia, ophthalmologic exam to evaluate for retinitis.

And then a newborn hearing screen, which should be repeated if failed, because there's many kids who failed that initial screen, and then when it's repeated in the nursery, it's not failed or BAER consistently failed. Next.

So treatment, you've heard a lot about this from our prior speakers, and we're going to talk a lot more about it. Next.

This -- and I just want to go through some of the things that come up very frequently that we still get asked.

So hyperimmune CMV immunoglobulin, there was a lot of interest in this in the earlier part of the decade, mostly based on the study in 2005, which was an uncontrolled clinical trial, which showed

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protection of hyperimmune CMV immunoglobulin to the mother versus symptomatic disease in both treatment and preventative groups of women and showed significantly increased specific IgG concentrations and avidity.

In that uncontrolled study, there were no adverse effects, and it really raised enthusiasm for the controlled clinical trials to follow, and that was published in New England Journal.

But in 2014, the randomized controlled trial by Revello's group showed no difference in incidents of congenital infection, clinical outcome of congenital infection when it occurred, no differences in virus-specific antibody, T-cell response, or viral DNA, and adverse events that occurred in higher rate in treated, which really dampened the enthusiasm. Next slide.

There was an additional randomized control trial in 2021, which was also published in New England Journal, which actually was stopped due to futility and the fact that there were adverse events in the treatment group, including severe allergic

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reaction in the higher incidents of symptomatic side effects.

So the -- the state of the art now is we do not use hyperimmune CMV globulin in pregnant women who have CMV disease. But it does come up in clinical practice. We get that question quite a bit. Next.

For antiviral, there have actually now been many groups that have looked at the efficacy of valacyclovir at 8 grams per day, either in a divided b.i.d. regiment or divided 2 grams four times a day for tolerability.

Most of these have shown no significant safety issues, and most of these have shown some effects. So for instance, Jaharmi's [ph] son showed a reduction in the PCR positivity in treated compared to non-treated women.

Jackomar [ph] showed decreased circulating fetal viral load, and Lorezbeil [ph] in 2016 again showed decreased fetal viral loads, as well as a reduction in a higher percentage of asymptomatic infants in those that were treated.

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And there actually has been a subsequent meta-analysis of these three, as well as some other studies, that concluded that this might be considered.

And I will say that we do offer this in our congenital infection program to women in certain instances, again, in a shared-decision model and with a careful monitoring for side effects for the mother. Next.

So "Postnatal Antiviral Treatment Trials to Define Standard of Care," this is the Collaborative Antiviral Study Group and now the more recent iteration in 2019 of the Congenital and Perinatal Infection Consortium, multiple centers across the U.S. and -- and where I really learned about this from, Dr. Kimberlin and Dr. Abzug -- next slide, also included international sites.

And to review the -- the pivotal postnatal antiviral treatment studies -- this was during my fellowship where -- when I started seeing children, we couldn't do anything for them, other than check for their hearing loss and do neuro exams.

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And after the CSG 102 trial, this was the randomized trial for six weeks of intravenous ganciclovir versus no treatment.

And there really was an improvement odds ratio of 5 for normal improved hearing in best ear at baseline and at 6 months in the treatment group, and the untreated group were more likely to have hearing loss at 6 months -- 21 -- odds ratio of 21 and 1 year -- odds ratio of 10.

A follow on neurodevelopmental study, these same patients showed that the treated had a fewer number of delays on their Denver Developmental Inventory. But the drawbacks and uptake of using IV ganciclovir were because of the need for prolonged PICC line, neutropenia, and potential risks of therapy.

So there are also concerns about the fact that viremia was suppressed on the -- the ganciclovir, but a rebound in viral load after stopping it, and the fact that we knew that the hearing loss is progressive.

So this really was laying the

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groundwork for the subsequent studies that suggested more prolonged suppression could be beneficial -- next slide, to both hearing and neurodevelopment.

And this is the pivotal trial that now has led to the standard of care of six months of oral valganciclovir. There was, of course, an intermediary study where the PK and dosing of valgan to achieve the levels that were achieved in the IV ganciclovir trial were figured out, and that is what was used in this study.

So this was six weeks versus six months of therapy, 16 milligrams per kilo, twice a day, which is what we use to this day. And at six months, there were no differences. But at 1 and 2 years, hearing was more likely to improve or stabilize in the six-month treatment group.

There were improvements on the Bayley nerve developmental composite and receptive communication scales, and less toxicity is seen compared to the IV therapy trials, and this was published in New England Journal. Next.

So this is -- I'm not going to go into

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all the details, because I think the other speakers have mentioned it. You know, there are many papers that suggest there's a consensus. But unfortunately, there's really no consensus still, because there's six different groups with six different consensus.

And, you know, to make it simple, if you have severe disease, no one disagrees. And if you have no disease, everyone agrees. But it's this middle thing that we have a hard time deciding.

And specifically, does sensorineural hearing loss isolate account as symptomatic or not? Even within a center, people will disagree on that and have differences about should the treatment be offered or not in the shared decision model or not.

And then most people agree, if there's only a mild or transient jaundice, for instance, that we would call that asymptomatic, but that if you had that in conjunction with a variety of other mild findings -- maybe three mild or moderate findings, that you might offer treatment. Next slide.

"Other Recommended Interventions." Once they come to us, we see them monthly to adjust

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their dose for weight, because this is a time of rapid weight gain, and to monitor toxicities while they're on their six months of valgan.

They get frequent audiologic evaluations, which again, different groups suggest different things. But we use every six months for the first five years of life, increased, of course, if there's abnormalities found. But if still nothing at five years, then annually until eight years.

We refer to early intervention programs. We have neurologic and neurodevelopmental assessments every six months to a year using the ASQ surveys.

We have follow-up with ID annually, and we act sort of as a home base for these families, because there are multiple specialists, and we always catch things that fall through the cracks and help them get plugged back in.

And then for children who do develop hypertonicity or spasticity or other problems -- motor deficits, physical therapy, and occupational therapy. Next.

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So the future -- this is my last couple of slides. If you go to clinicaltrials.gov, there's 61 trials that are U.S. and international that have focused on or are currently focusing on congenital CMV. And I break these into those that target the prenatal period and those that are postnatal.

So for prenatal, the areas are identification of fetal or prenatal biomarkers, including maternal viral load, cytokines, genetics, and using proteomics to do so.

There are also prenatal intervention and treatment trials that talk about behavioral modification, prevention with vaccine, the passive immunity trials that we've already talked about, and then the antiviral therapy, valacyclovir, already mentioned, but also letermovir. Next slide.

And then targeting the postnatal period, there are studies that are focusing on screening, both the targeted and all children universal, and then a long list of things that are being looked at for postnatal, including monoclonal/cytotoxic T-cell lymphocyte therapy,

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expansion of valgan treatment to asymptomatic infants, and then use of letermovir, which the Congenital Perinatal Infection Consortium is currently doing as an adjunctive therapy, and we're all very excited about.

And then expansion of treatment beyond the neonatal period, which has been alluded to, because families ask for this.

The study that was just completed by the Collaborative Antiviral Study Group did try this. We had a low end and did not see differences in hearing outcome. But -- but as you've heard, other studies have potentially shown a benefit, and that has led to the change in the recommendations that perhaps we can treat, at least out to 3 months of age. Next.

So I just want to acknowledge all the people that work in the Children's National Congenital Infection Program, particularly Sarah Mulkey, who is our fetal prenatal and neonatal neurologist, and Dr. du Plessis, who leads that division.

And I will end there.

DR. HODOWANEC: Thank you, very much,

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Dr. DeBiassi.

Next, I'd like to introduce Dr. Megan Pesch, clinical assistant professor, director of the Congenital CMV Follow-up Clinic in the Division of Developmental and Behavioral Pediatrics, Department of Pediatrics at the University of Michigan.

We are thrilled to have Dr. Pesch join us today to provide us with her unique perspective as both a pediatrician and a congenital CMV parent.

In her talk entitled "Living with Congenital CMV - Parent Perspective," Dr. Pesch will provide not only her own perspectives, but those of other congenital CMV parents, some of whom participated in our recent FDA-sponsored Congenital CMV Focused Patient Listening Session.

Thank you, so much, for joining us today, Dr. Pesch.

DR. PESCH: Thank you. It is an absolute honor to be here. I'm going to start out -- actually, if you could advance to slide 4. There we go. Oh, back one. I guess it was 3. Thank you.

So we're going to start out with an

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exercise. I want to have you all imagine and put yourselves in the shoes of our CMV families.

So let's just take a minute and imagine that you are pregnant with your third baby. This might be more of a stretch for some of the people on the call than others. But just go with it.

First, you have had two healthy babies already. They're at home. They're toddlers. You're exhausted. But otherwise, gosh, this pregnancy is going super well. You are doing absolutely everything your doctors tell you. You're taking your vitamins. You're going to all the appointments. You don't scoop the kitty litter, eat sushi or lunchmeat. Next slide, please.

And when your baby is born, it's a girl -- your third girl. What a joy. She is perfect and absolutely kissable. There are a few dots on her face, and actually, she did fail her newborn hearing screening. But you're told it's likely fluids, and you have heard that before too, so you're not very worried. Next slide, please.

You take her home and just love on this

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perfect baby girl. She's the final member of your family, and everyone is absolutely overjoyed. You have two and a half months with her until your world comes crashing down when you find out that she has profound hearing loss.

And your soul is absolutely crushed when you hear from the otolaryngologist that she has likely never even heard your own heartbeat.

You have no idea what's going on. Even in utero for those last few weeks, everything seemed to be going perfectly well.

You ask a bunch of your friends and doctors and around 4 months old, find out that this is congenital CMV, something that you had heard of maybe in the past, but not really. It's only a vague memory, and actually, just the C in that TORCH acronym.

You -- imagine how you feel when you find out that if you had been in another part of the country or another part of the world, that you would have been counseled about how to avoid this virus during pregnancy; and had you been somewhere else, you

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possibly would have been tested for this virus during pregnancy; and had you lived in another part of the world, you may have been offered treatment for this virus during pregnancy; and if your baby had born just another state over, she would have been tested for this virus and offered treatment.

Imagine that sense of betrayal, that sense of anger, and that sense of pure devastation when you realize all of these missed opportunities have happened to you and your family.

Now, of course, this is my story. But this is a story of so many CMV families, and I think it's really critical that we hear their words today and try to put ourselves in the shoes to understand the huge impact that this virus has on the life of not just these babies, but those who love them. Next slide, please.

So this -- this is my daughter. Her name -- is perfect. Our journey has been long. She was -- like I said, identified at 4 months, too late for antiviral therapies. Although, we did them anyways.

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She has bilateral sensorineural hearing loss, global developmental delay. Next slide, please. She's also autistic, which I have to say, some of my favorite things about her are due to her being deaf and autistic. So it's a bit of a mixed bag.

During her first year of life, these were all the therapies she went to. She was a busy lady. So she had three to five appointments every week with therapists and all of these subspecialists. Next slide, please.

This is me and just a bunch of CMV moms. I love this picture, because it was the week before the pandemic hit, and we were all in Denver at -- or no, we were -- not Denver. Well, we were at a conference, and we were hemming and hawing, like, oh, I wonder if this COVID thing will be difficult. Yeah, it turns out it was. Next slide.

So that's a little bit more recent picture of Odessa [ph]. Like I said, she's autistic. She -- her world is completely different than mine. The apple really has fallen far from the tree. Although, it has been just an absolute joy and wonder

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to get to experience her world.

It's tricky, because I love her more than life itself, and yet, what this virus has done to her brain in utero, you know, it's not -- it's -- it's undebatable that it has really changed the course of her life and made things much more difficult for her. Next slide, please.

Our family moved -- has had to move states to get services for her from Ann Arbor, Michigan, to St. Louis, Missouri, and then on the next slide, you'll see that we came back -- next slide, please, two years later, and now she goes to school in a whole different community in Michigan, because of some of the hardships we've faced in trying to find just the right therapy for her. Next slide, please.

There she is now. I mean, look at that face. Next slide. I can't help, but brag, you know. So let's talk about the perspectives and families with congenital CMV.

So starting out in pregnancy, it's a fact that in this country, the vast majority of pregnant people are not counseled about CMV.

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ACOG does not recommend it. And it's not that they omit the recommendation. They recommend not educating about congenital CMV prevention in their bulletin, because they state that it -- the implementation of such measures are likely burdensome and impractical for women to implement, which I strongly disagree with.

Sometimes moms find out due to imaging abnormalities. Unfortunately, many physicians are misinformed about how to -- how to incorporate antibodies, which we heard in a prior presentation is not always very straight forward.

And people have presented with specialist referrals when CMV is diagnosed in pregnancy. Although, often there are limited options presented in terms of treatment. Next slide.

So "Treatment and Pregnancy, What Does This Look Like?" So in the U.S., generally antivirals are not recommended by the book. Although, there are some places that will offer them.

A lot of mothers, I see turn to other mothers online. So there are some very active social

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media groups, CMV Mommies and CMV Awareness in Pregnancy, are two of the Facebook groups that have thousands of members.

We -- I see moms asking other moms which providers are antiviral friendly, "Who will even talk to me about antiviral," and mothers will travel to different providers, just to have that conversation.

I know at my institution and many others, termination is frequently offered before antivirals are offered, which is a tough pill to swallow if this is a pregnancy that is very much desired. New -- new slide, please. Next slide.

So here are some quotes, and these are paraphrased from social media, so even if you search them, you won't find exactly the person.

"I'm so thankful for this online community. There is such a depth of knowledge from this group. I'm really just thankful for -- I'm really just thankful for it. None of the doctors know what to do. But I'm the one bringing them ideas from this group."

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"My doctor said we can't do antivirals. I'm so scared about what's going to happen. Does anyone know any maternal fetal medicine specialists in "blank" City who will at least talk to me about antivirals?" Next slide.

Then once the baby is born, there is often a diagnostic odyssey. If the baby has a diagnosis of CMV right away, the path is a little bit more straight forward. Although, the unknowns are plentiful.

Many families are launched into this unexpected role as medical parents. And like I mentioned in my intro, there is a feeling of anger and being betrayed by the medical system. I think it is somewhat less if the baby is identified early on.

But the feelings are still there, especially in terms of being directed towards the OB/GYN community, who parents, you know, perceive maybe didn't tell them, and, you know, could this have all been prevented -- or prevented. The what-ifs and could-haves and if-onlys are -- are abundant.

And in infancy, a common thing that we

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see in social media and I see in my own practice, is that these precious moments are lost. You know, in hindsight, I had two and a half months before I knew my daughter was deaf.

And, you know, I like to be a glass-half-full person when I can. I -- I had two precious -- two and a half precious months with her where I wasn't overwhelmed with this possibility of what CMV would be bringing into her life, and so for that, I'm -- I'm grateful, even though if I could do it all again, I certainly would have gotten her antivirals early. Next slide.

Here's some quotes summarized from the FDA parent listening sessions. "The hardest thing is the lack of awareness and knowing that we were not given the knowledge to prevent this." "We were robbed of the ability to try to reduce CMV in pregnancy." Next slide.

These are quotes paraphrased in social media. "By the time we found out about her CMV, it was too late for treatment." "We saw so many specialists. He got so many tests. We were told that

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he probably had a fatal genetic condition. No one ever mentioned CMV." Next slide. Let's skip this one. Thank you. Next slide.

There's also a lot of misinformation and discrimination out there. I think medical professionals, people in the community hear "infectious disease" and often think that CMV is -- is so contagious, like COVID or maybe even more.

A lot of our families report that they are isolated, and this kind of adds to the trauma, I would say, of having this diagnosis in infancy.

"The nurse literally ran out of our room when she found out our baby had CMV. She said she was expecting and couldn't take the risk of caring for our baby."

"My infectious disease doctor told me that I should keep away from other people. She was wearing a full Tyvek suit when we were talking -- when we were -- when she was talking to me. I walked away from that appointment thinking I had a serious infectious disease and was at risk to her and other people."

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And this, of course, is -- is not true. CMV is transmitted through bodily fluids and not through casual contact or respiratory secretion. Next slide, please.

"My son was kicked out of daycare, even before he started. The daycare director called the state health department, and they told her my baby was a risk to their staff. We don't tell anybody about his diagnosis anymore. We've been shunned too many times. I want to be open. But I do not want him or my older child excluded from other activities or social opportunity."

And these are, quote, "summarized" from Instagram. New slide -- or next slide, please.

So family life, these are partially taken from the family listening session, partly taken from a paper I wrote with Shelly Zappas and Amanda Devereaux, two medical CMV moms.

So a lot of families feel, like, they have to just educate by existing. So many people haven't heard about congenital CMV, and having to explain over and over can be exhausting.

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"Every single part of our lives has been affected. There are so many little things," is a quote from one family.

Often, families report leaving or changing employment. There's stress on marriage. Siblings often feel left out or become glass children -- those children that get looked right through when there are other kids with higher priorities in the family. New -- next slide, please.

In early childhood -- oh, I'm sorry. Next slide. I think these -- this is the older version of my slides.

So there's also the fear of the unknown. "We live in anticipatory fear wondering what else will happen; when will her hearing get worse; what will -- will there be a point when we can't control her seizures; what will life be like for her when we're -- around? In some ways, I hope we outlive her." Next slide.

I wanted to end by sharing Dakota's story. Dakota was a little girl who lost her life to congenital CMV. She was just over 1 month old.

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Her dad reached out to me on social media, and we had some nice conversations, and he -- he said I could use these direct quotes.

"If we'd known about CMV earlier, we could have made decisions as parents for her. But the medical system made those decisions for us. We both worked in healthcare, and we had a 2-year-old at home. No one said anything.

I'm still mad, because we were in a large medical center in "blank" City. There's lots of resources, and it seemed everyone just didn't want the liability of treating a pregnant woman. We are both pharmacists. We understand the risks better than anyone." Next slide.

"When she was born, we were told she had a one-third chance of being deaf. No one told us the whole truth about how bad CMV could be. And Dakota had the worst-case scenario.

I felt, like, the whole 34 days she was in the NICU until she passed away, no one was ever completely honest with us." Next slide.

"We recently passed a law in Washington State. I'm willing to answer any questions you have. I just want to continue being a parent to my daughter, even though she's not here. I will help however I can."

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And I think this sentiment is really -- really rings true with so many CMV families. They are devastated. But they want to help. They want to help the next generation.

And I think it's really important to remember all those babies and pregnancies that were lost to CMV. We spend so much time talking about the hearing loss and the cerebral palsy, which certainly are significant. However, the impact on lives is much -- much greater than just those two things. Next slide, please.

So in summary, CMV is the worst. But our kids are absolutely the best. We desperately need more awareness, and families deserve answers and treatment, and lives are lost to the lack of knowledge and lack of treatment for congenital CMV. Next slide.

Thank you.

DR. HODOWANEC: Thank you, very much, Dr. Pesch. That was such a -- a powerful and moving presentation. We really appreciate you taking the time to share so openly your family stories and those beautiful photos of your family. It -- it really means a lot to us that -- that you were with us today to -- to share that.

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In just a moment, we are going to open up for clarifying questions and comments pertaining to these sessions we've heard -- these presentations we've heard in the first session.

Before we do so, I do want to just mention, if anyone is interested in hearing additional quotes or -- or summaries from the patient listening session that was conducted here at FDA, those are -- there's a summary posted online.

If you just Google "FDA patient listening sessions," you can search for the one on congenital CMV, and there's lots of, I think, really enlightening discussion and content there.

So with that, again, we will open it up briefly for clarifying questions and comments. So parent -- or panelists, please raise your hand in Zoom

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if you wish to ask a question, and members of the public may enter questions into the Q&A box.

Okay. I think, Dr. Bo, you had a question or comment?

DR. BO: Thank you, very much, for the opportunity. We greatly appreciate Dr. Pesch's -- such a moving presentation and Dr. Lanzieri's slides and DeBiasi's very informative presentations.

I have a question in regards to -- maybe a clarifying question, and potentially, maybe we can extend it into the panel discussion later on if it's -- time doesn't allow.

But one of the questions that we're interested in asking is, how much of the clinical manifestations related to CMV are originating from the infection during gestation versus newborn? Thank you.

DR. HODOWANEC: Thank you for that question.

Dr. DeBiasi, would you like to address that?

DR. DEBIASI: Yeah. I -- I mean, it really depends on which clinical manifestation. So

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for instance, like, if it's polymicrogyria, which implies that it was an early in utero insult to the neurons as they were trying to migrate and go where they're supposed to, you know, that injury is irreversible. So an antiviral treatment will not be able to reverse polymicrogyria.

On the other hand, the hearing loss, which is progressive, that might be a combination of both viral effect, as well as an inflammatory response that's happening in the vestibular area.

So it's really kind of variable, depending on what the manifestation is. I hope that answers your question.

DR. HODOWANEC: Thank you, very much, Dr. DeBiasi. Oh, Dr. Schleiss, yes?

DR. SCHLEISS: Oh, well, I -- I would just add, I mean, if the question is, you know, does postnatal acquisition of CMV or acquisition during labor and delivery in the birth canal, which can happen probably rarely, does that lead to sequelae in babies?

I mean, there is a literature, of

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course, on low birth weight and extremely low birth weight premature infants acquiring CMV in the NICU setting, most commonly from breastmilk, and certainly, it can cause short-term disease.

Whether it can cause long-term disease, including hearing loss, is unknown. There are some papers that suggest that extremely low birth weight preemies may have some long-term risks. Certainly, they can have short-term disease.

The whole issue of whether or not a strategy should be adopted to prevent acquisition of CMV in premature infants in a NICU setting is one that's actively being researched in many centers.

But I -- you know, if the question is, does intrapartum or postnatal acquisition of CMV disease happen? Yes, but most commonly in preemies.

DR. HODOWANEC: Thank you, very much, Dr. Schleiss. There's a couple of comments in the public Q&A box that I'll just share with the larger group.

The first commenter says, "That was a very powerful -- that was very powerful, and really

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appreciate sharing of all those quotes from parents. It is so important to involve parents in decision making and give that knowledge about this disease.

The quote that the medical system made that decision for us was so powerful and something we should all keep in mind." Yeah, thank you, very much, for sharing that Alyssa [ph].

And then we also have another comment noting that this is sort of congenital rubella dþjþ vu and commenting that they hope we have an effective vaccine soon, which would be -- would be wonderful.

And then we have just a couple of minutes left, and there's a question now in the Q&A box. And the question is, "If the severity of congenital disease varies by trimester, is there an argument for first-trimester screening?"

And I don't know if Dr. DeBiasi or Dr. Schleiss would like to tackle that one.

DR. DEBIASI: I'm going to leave that one to Dr. Schleiss.

DR. SCHLEISS: Well, yeah. I -- I was hoping you would answer it, Roberta. I mean, I think

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the answer is, yes, there is a very powerful argument to be made for first-trimester screening, and I would hearken back to my slide from the Canadia Obstetrics and Gynecologic Association.

I -- I would like -- I would hope that ACOG would tackle this issue in some earnestness in the -- in the coming months and years.

You know, the -- the dilemma is that in comparison to Europe, I think there are more pregnant patients in the United States who may not be aware of their pregnancies early enough in gestation to offer a window of screening and, as we heard, possible intervention with antivirals.

But I think this whole issue of maternal screening is -- is something we -- we need to -- to really think about.

And I would call attention to a provocative, I think, very interesting paper from Brigitte Faas' group that was just in eBioMedicine that -- that exploited the use of noninvasive prenatal genetic testing, which is often done to screen for aneuploidies and -- and to look for -- for CMV and by

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DNA -- PCR, and Dr. DeBiasi had a brief mention about it in one of her slides as well.

I think that's an important area for -- for future -- future research as well.

DR. HODOWANEC: Thank you, Dr. Schleiss. And -- and we -- actually, we have a follow-on question to that, which is, do all first-trimester exposures show ultrasound findings?

DR. DEBIASI: No. Yeah. The answer is no.

DR. HODOWANEC: Thank you, Dr. DeBiasi.

DR. SCHLEISS: Yeah. Ultrasound is imperfect. There's certainly plenty of babies with severe CMV disease who have normal antenatal ultrasounds.

Now, when I'm evaluating these babies clinically, I always ask particularly about the 20-week ultrasound, which almost all pregnant patients will get a 20-week ultrasound.

The most common fetal ultrasonographic abnormality in cases that are documented is echogenic bowel, actually. But there are lots of examples of

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ultrasound being normal in babies that end up infected and affected.

DR. HODOWANEC: Thank you, Dr. Schleiss.

Dr. Pesch, I know you had started to come off mute there before. Did you have any comments that you would like to make?

DR. PESCH: Oh, I just wanted to say that I'll -- I'll pass that along to Dakota's dad, the -- those nice comments.

DR. HODOWANEC: Thank you, very much. I'm sure that would be appreciated.

And then this will be the -- the last comment. I see that Dr. Bo has his hand raised again, and then we will be going to break.

Dr. Bo?

DR. BO: Yes, thank you, very much. Very quickly. Thanks to Dr. DeBiasi for -- for your response. It makes complete sense what you are saying.

Somewhat related to what you had presented with regards to monitoring -- CMV PCR

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monitoring, where there isn't really a standardized well-accepted viral load in order to initiate treatment.

And I'm wondering, is one-time CMV PCR -- is enough to catch the viral load kinetics and the movement of the -- of the virus throughout the -- the infection process?

DR. DEBIASI: Yeah. I mean, your -- your question is excellent. And Dr. Kimberlin is the expert on this. I mean, this is, you know -- in parallel, we didn't have time to talk about it. But the studies that have been done to look for treatments also have viral monitoring aspects of these.

And there is a lot of variability in both untreated, as well as treated infection, which probably relates to both antiviral effective whatever medications we might be using, but also the host immune response, which is, you know, variable. So it's very complicated.

DR. BO: Agreed. Thanks, so much.

DR. HODOWANEC: All right. Thank you, very much, again, to all of our Session 1 presenters,

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and thank you for all of these great questions and comments. We will now go to a break, and we will return for Session 2 at 10:40. Thank you.

(Off the record.)

DR. HODOWANEC: All right. Welcome back everyone. We will now begin Session 2, which will focus on congenital CMV drug development considerations.

During this session, we will hear from Doctors Emma Mohr, Lindsay DeVries, Ryan Kau, Megan Pesch, and Rachel Greenberg.

It is now my pleasure to introduce Dr. Emma Mohr, assistant professor in the Division of Infectious Diseases, Department of Pediatrics at the University of Wisconsin Madison. Dr. Mohr will be discussing preclinical models of congenital CMV infection.

Thank you, Dr. Mohr.

DR. MOHR: All right. Thank you, very much. So I'm going to change the talk about humans for a little bit and jump to a discussion of rhesus macaques and the model of congenital CMV infection in

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them. All right. Next slide, please.

So rhesus macaques are a model of human pregnancy and congenital CMV infection. They're probably the model of pregnancy and fetal neurodevelopments that most closely mimics humans of all the animal models out there.

So one of the reason that they are considered a good model is that placental transmission of species-specific CMV occurs in both of these species. Fetal sequelae on the brain, including ventriculomegaly, leptomeningitis happens in both species as well.

Rhesus macaques develop antibody responses during pregnancy, just like humans do, and T-cell responses are important in both rhesus and human pregnancies.

CMV species are different between these two, human and rhesus macaque, though. So when rhesus are used for models, they have to use a rhesus-specific CMV, which is endemic in colonies of rhesus macaques all around the country.

This rhesus is very similar in sequence

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to human CMV, and the gB glycoprotein antibody targets are very similar between the two, so it's thought to be a good model of the CMV species as well. Next slide, please.

So in the mid-80s is when CMV models started to become developed in rhesus macaques. So the first model did an intracerebral inoculation in the fetal brain in the second trimester. And this what the histology looked, like, of the brain. You can see ventriculomegaly, and leptomeningitis was present as well. Next slide, please.

So the rhesus models have moved beyond just looking for infection and -- and brain -- brain abnormalities. I'm going to talk about today model -- modeling congenital CMV infection in pregnancy, studying postnatal CMV and transmission, and then really the lack of studies of infant outcomes following any of the prenatal infection models. Next slide, please.

All right. So one of the first studies I'm going to talk about is a study that was done in pregnant rhesus macaques, and this was looking at how

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C4T-cells are important in protecting against severe congenital disease.

So before this, there had just been a few animals that were inoculated with CMV and looking at infant -- or sorry, fetal outcomes, like brain abnormalities. This was the first study to really increase the sample size and look to see sort of more broadly what happens to the fetuses.

So there are two groups in this study. In Group 1, they depleted the T-cells right before inoculation with C -- rhesus C and B during pregnancy. And that's Group 1 in the top.

You can see it both in red, the viral loads of the plasma, and then in blue, the amniotic fluid viral loads. Three of the four pregnant animals that were T-cell depleted and had rhesus CMV inoculation had fetal loss. The other animal had documented virus in the amniotic fluid still.

In Group 2, those were immune competent animals, and they were inoculated with rhesus CMV as well. One of the infants that was liveborn had pancytopenia. The liveborn infant in the T-cell

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depleted group had intrahepatic calcifications seen on ultrasound and then neutropenia found after birth. Next slide, please.

So this model was expanded, because they really wanted to see the phenotype and see if they could rescue the phenotype with hyperimmune globulin therapy.

So the question was, does hyperimmune globulin therapy improve pregnancy outcomes in the severe phenotype of CD4T-cell depletion in this rhesus macaque model.

So they had three groups. The first group did the T-cell depletion, followed by rhesus CMV inoculation at the end of the first trimester. They had two different hyperimmune globulin groups.

The first was standard HIG, which they applied right after the T-cell depletion and then an hour before inoculating with rhesus CMV. And this HIG was defined as a good binding against the rhesus CMV.

The high potency HIG, in contrast, these -- this preparation was found by good neutralizing antibodies to epithelial cells, so

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slightly different definition of what -- of what the antibody was.

And again, the timeline was T-cell depletion and then a week or so later, administration of the HIG product by inoculation with the rhesus CMV. Next slide, please.

So again, they're looking at sort of very black and white outcomes here, just seeing if vertical transmission was seen by looking at CMV in amniotic fluid.

So the top, those are the controls. You see virus in the maternal plasma. You see virus in the amniotic fluid in all of the animals, and then variable levels of virus in the urine and saliva.

And in the standard HIGs, these similar things, vertical transmission or detection of virus in the amniotic fluid was -- didn't occur in all the animals. It occurred in two-thirds of the animals.

And in the high potency HIG administration, you see that vertical transmission of virus to the fetal compartment where virus is detected in the amniotic fluid was blocked.

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So here, inoculation of -- or treatment -- pretreatment with HIG before infection with rhesus CMV was protective. Next slide, please.

So this was a very interesting model. But it's hard to say that this is a really good model for human studies, because there are no T-cells around. So how often does this mimic what happens -- happens in human pregnancies?

So another study was done looking at vertical transmission in immunocompetent pregnant macaques. And here, they did a similar setup where they're inoculating right at the end of the first trimester, doing lots of different maternal blood draws, weekly amniocentesis to look for vertical transmission to the fetal compartment, and then the fetuses are harvested toward the end of pregnancy.

So the graph there in B shows the maternal plasma loads with the comparison between the amniotic fluid positive and amniotic fluid negative animals. Really, you can see that they overlap a lot, and they have other graphs that show there were no significant differences in the patterns of maternal

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viral loads between the amniotic fluid positive and negative animals.

Of the 12 animals that were infected in this group, only 5 had transmission of virus to the amniotic fluid that was detected. So it's not 100 percent vertical transmission in the model where CD4T-cells are depleted. Next slide, please.

All right. So now, I'm going to jump to the other side of this. So there's been a lot of the model development in the pregnancy side of this, but not as much in the infancy side.

And the infant side has really focused on postnatal CMV acquisition, so it happens naturally, and if you can establish a model of postnatal CMV infection in infants. There have not been any studies of antiviral treatment of prenatal CMV infection in rhesus macaques. Next slide, please.

So one of the earliest studies to look at, sort of a postnatal CMV model in rhesus macaques was to look at CMV oral inoculation in rhesus macaques.

So here, 4-week-old rhesus infants were

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inoculated orally, so just a syringe with -- with CMV, and viral loads were measured in their urine, plasma, and saliva for a year afterwards.

For comparison, they also inoculated five adult rhesus macaques orally as well and did the same sort of studies. So the adults are in black, and the infants are in -- in gray.

So this graph shows the antibody responses to CMV after this inoculation. So all of the infants develop antibody responses within a short period of time after inoculation, so showing that the inoculation really worked to establish a persistent CMV infection.

The adults had variable responses. Some required multiple inoculations to have a successful infection. Next slide, please.

So another big question that has faced rhesus macaque researchers is -- is when CMV is naturally acquired in colonies. So it is widespread. But it's unclear when exactly in that sort of infancy, early child -- early -- early years of life CMV is acquired.

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So this study looked at where CMV was in 1-year-old macaques, 2-year-old macaques, and 3-year-old macaques. And what they found was that looking at 1-year-old macaques, there is not much virus that's found in many of the macaques in the urine, saliva, or the plasma.

But by the time that they're 2 years old, all of the rhesus have virus detected in the urine and saliva and some -- some in the plasma. And they see the same thing at 3 years old and adults as well.

So this suggests that sometime after they turn a year old, after that weaning period, is when they naturally acquire rhesus CMV infection. Next slide, please.

So another question that was addressed by rhesus macaque study was trying to understand if breastfeeding transmission of CMV occurs naturally in the rhesus population.

So what the study did was paired CMV-positive moms with their infants that they -- that they just gave birth to and measured viral loads in

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their breastmilk, saliva, and urine, and then infant saliva over the first six months of life.

So Mom's breastmilk had variable levels of CMV found over the first six months of life of the infants. Mom's saliva also had some CMV detected at many different time points. The urine of the -- the dam as well showed variable levels of CMV throughout this time, and then infant saliva showed very sporadic levels of CMV positivity.

So this is interesting. So it didn't go up and stay up. And I have a graph on the next slide to show you that the researchers thought that this was sort of sporadic shedding, not a persistent infection that was established.

So these are those same infants that had the sporadic shedding of CMV in the first six months of life. But you don't start seeing CMV-specific IgG detected until after a year of age.

So they didn't have any CMV IgG that was their own and not transplacentally transferred from Mom until very much sort of, you know, 15 months or so of life, after they were weaned and after they

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were group-housed with other infants.

So what they think here is that rhesus macaques probably don't transmit by breastfeeding very often. It's probably more interactions after that breastfeeding stage where they acquire natural CMV infection. Next -- next slide, please.

All right. So this is my summary slide here. So there are multiple congenital CMV models in pregnant macaques. CMV infection is variable in immunocompetent macaques.

The other finding was that maternal T-cells are really protective in helping against severe congenital disease, which includes fetal demise and preventive hyperimmune globulin blocks vertical transmission.

In infants, it's really postnatal transmission that has been evaluated. What they found is that infants are susceptible to CMV infection by oral inoculation. CMV infection naturally occurs in rhesus macaques by about 2 years of age, and then breastfeeding CMV transmission probably doesn't occur very commonly.

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So what are the sort of open areas in the rhesus macaque model for studying congenital infection?

So one of the limitations is that congenital infection is -- is variable in these immunocompetent dams. So studying antiviral therapy and offspring would be challenging when you don't have every infant that's actually infected.

And given the small sample size that you need to have in these studies for cost and limitation of animal numbers, that would be very challenging.

Fetal tissues for these studies have really been prioritized for viral studies, rather than any developmental studies.

Again, probably because we're looking for a very strong phenotype where you can see viral positivity or not, rather than looking at infant development studies over the first year of life.

So while there are many challenges to infant outcomes and treatment in the macaque model, I think there's lots of room to help answer questions

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that maybe cannot be answered in human studies.

Thank you.

DR. HODOWANEC: Thank you, very much, Dr. Mohr. Very informative.

Next, I'd like to introduce Dr. Lindsay DeVries, a scientific reviewer in the office of product evaluation and quality in the Center for Devices and Radiologic Health here at the FDA.

Dr. DeVries talk is entitled "Congenital CMV and Hearing Loss: Study Design Considerations." Thank you, Dr. DeVries.

DR. DEVRIES: Hello. Can you hear me okay? If so, we can go to the next slide.

DR. HODOWANEC: Yes, we hear you. Thank you.

DR. DEVRIES: Okay. Thanks. Sorry.

Okay. So today, like, Aimee said, I'm going to be talking about study design considerations. I know that we've been touching on that a bit in this workshop, so I'm going to try to bring it together from an audiology perspective.

So I'm going to talk just briefly about

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the characteristics of hearing loss in general and in congenital CMV, a little bit about hearing assessment in the pediatric population, and then get into the considerations for study design. Next slide.

So we'll start with hearing loss in the audiogram. This is something that -- next slide, most of you probably know a little bit about, but maybe not everybody, so I want to walk through it.

So there are three main types of hearing loss that audiologists typically treat. There's sensorineural hearing loss, which is the most common hearing loss that you see in older adults. But obviously, you see it in children as well.

And that is hearing loss due to pathology in the cochlea, the auditory nerve, or even the central nervous system, and it is typically permanent in nature. These are the people you often see wearing hearing aids, cochlear implants.

Conductive hearing loss is typically an abnormal mechanical transmission of sound, getting from the external or middle ear into the inner ear, so things like an ear infection, some kind of blockage,

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often can be treated with medication or surgery. But sometimes people do have hearing aids when they deal with these chronic issues.

And then a mixed hearing loss is just what it sounds, like, a combination between a conductive and a sensorineural hearing loss, which can occur when people have chronic middle ear issues, and as they age, they may get some more permanent hearing loss, so we see that too. Go ahead to the next slide.

So this is just one example of the degrees or severity of hearing loss that we -- that we treat, and this is how we categorize them. There are different entities that have slightly different ways of doing this, so this is just one example.

But we typically categorize severity of hearing loss as normal, sometimes slight, mild, moderate, moderately severe, severe, and then to profound. So it can kind of range the whole gamut of the audiogram, which I'm going to go over here in just a moment. So you can go to the next slide. Okay.

So we'll break this down a little bit. We'll slow down for just a second, in case it's been a

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while since some of you have seen an audiogram, if ever. So this is a little busy. But we'll break it down.

On the X axis at the top is frequency, so from low to high frequency or more base sound to a more treble sound. And on the Y axis is the decibels or amplitude from a soft sound at the top of the graph to a loud sound at the bottom of the graph, so as you move down the graph, the hearing loss is more severe.

And so this is just one example that shows what we call the "speech banana." So you see that blue kind of banana-shaped circle in there with the letters in there?

This is an audiogram that people will often use in pediatric clinics, because it emphasizes the frequency range of specific sounds, more high-frequency sounds, like, S and F, and lower frequency sounds you can see, you know, like, Z and V, M, D, B. And so this is a great counseling tool for parents.

The blue marks here are indicative of the left-ear hearing status. So you can see as you go up in frequency, the -- the threshold increases,

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meaning it gets worse. And then the right ear is in red, which shows a much more severe hearing loss.

These are just, like I said, examples. But I'm going to be showing you a couple audiogram-like figures later. So I just want to make sure we're on the same page.

But this is the audiologists' kind of major tool. But we have a lot of other assessment tools that we use, of course, otoscopy and looking in the ear, tympanometry, and acoustic reflexes, looking at function in the middle ear, and otoacoustic emissions, which we'll talk a little bit more about later, which are one way to measure some inner-ear function.

And I just want us to keep in mind, especially in the context of CMV, that there are other hearing loss characteristics. So you can have unilateral hearing loss, hearing loss in one ear, or in both ears. It can fluctuate. It can be progressive.

As you see on the graph to the left here, it can be asymmetrical. So two ears can be

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doing two different things, which is also something that can happen in CMV. So just keep in mind it can be a little bit all over the map. So let's go to the next slide.

Right. So I found this great recent review on congenital -- hearing loss in congenital CMV. So I -- I've kind of compiled some of the takeaways from that, because I thought it was really useful.

So just at a high level, congenital CMV is responsible for hearing loss in 20 percent of children that don't have any other risk factors for hearing loss. So that's, you know, that's a pretty high percentage.

One of the key takeaways, I think, from this talk and others is that CMV-related hearing loss tends to be highly variable. So it's often sensorineural in nature or typically, and it can occur in symptomatic or asymptomatic cases. But there are some differences.

So this type of hearing loss is often more severe is symptomatic cases. And it's often both

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ears in symptomatic cases, whereas in asymptomatic cases, it's more often seen in one ear.

The poorer ear, if you have hearing loss in both ears, often "worses" earlier and faster than the better-hearing ear. So even if you have hearing loss in both ears, if one is worse than the other, it tends to kind of degrade and get worse faster.

Irrespective of middle-ear conditions that kids can get, like ear infections, the hearing loss, the underlying potentially permanent hearing loss, can fluctuate. So it can -- it can look better; it can look worse. So it's -- it's a little tricky.

It can also progress over the years. So the risk tends to reduce after the age of 5. But that doesn't mean that your first audiogram will look, like, your audiogram at age 4 or 5. So that's another thing to consider.

And it can be late onset. So I think somebody had mentioned a late onset case earlier today, early yesterday. But in 10 to 20 percent of cases, at least in the literature, there is a late

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onset. So you can see looking through here, it's -- it's very hard to pin down. You can go to the next slide.

Okay. So I don't want to read this at you. But there was a study done. It's about ten years old now. But it's a pretty good study that looked at, kind of at a high level, the -- the rates of asymptomatic and symptomatic children and it kind of broke down their hearing loss characteristics.

So this study looked at 68 children. You can see here 59 had symptomatic CMV and 9 -- that's a typo; 59 had asymptomatic CMV, and 9 had symptomatic. Sorry about that.

So of the asymptomatic children, that bigger cohort, there was hearing loss to be seen. So 16 had sensorineural hearing loss at their first visit and 11 at their last visit in the study, basically meaning that some of them had unstable thresholds, and 5 of them had fluctuated back up into a more normal range, but unclear if it would fluctuate again.

So this is just kind of a snapshot in time. Of the -- of the symptomatic children, six had

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sensorineural hearing loss at their first visit, and five at -- five ears at their -- had sensorineural hearing loss at their first visit and five at their last visit.

So fewer kids in this group, and only one of them fluctuated back into the normal range. But you can kind of see that most of the kids still had hearing loss.

And so the takeaway here is, of all of these kids that had hearing loss at their last visit in the study, ten of them had unstable hearing. And I know this isn't adding up to 16. I keep forgetting it's ears, not necessarily kids. Sometimes we break it down between ears, which we'll talk about later.

But ten had unstable hearing, and then seven ears had instability exceeding 30 dB. So 30 dB is a pretty substantial fluctuation. You're -- you're moving those severity categories quite a bit.

So 32 percent of the kids -- they did them as meta-analysis, had sensorineural hearing loss and -- or in the study, and 29 percent had unstable thresholds. So not everybody had unstable thresholds.

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But -- but a good chunk did. And I'm going to show you. This is a lot. So I'm going to show you just a couple examples on the next slide.

So these aren't the best quality. But I really -- I really did have trouble finding some nice pictorial representations of audiograms in the literature, for some reason.

But what this is showing here is not exactly an audiogram. On the X axis is time. So we're going to be looking, you know, out -- in the first case, up until they're -- what 12 years old and the other case here 5 years old, so they followed these -- some of these kids a long time.

And on the Y axis, again, is decibels from at the top, more normal hearing, to at the bottom, more profound hearing loss. And the Xs in both cases are the left ear -- yes, in this case they are. It's a little different from how we would do the audiogram.

But the squares are the right ear -- or I'm sorry, the other way around. Squares are the left ear, and the Xs are the right ear. It throws me off,

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because audiologists do it a little differently.

But in any case, it doesn't matter which ear is which. You can look at the -- at this at first glance, and you can see that the ears differ, you know, some hearing loss at some frequencies, not at others, and over time, that will change in each ear, but not necessarily in both ears.

So it's a little all over the map. And if you go to the next slide, it's the same thing. You can see here these kids are a little bit younger. But they tracked them out 30 months, 39 months, and you can see that there's some stability there, and in some cases, it got worse and stayed worse, and in some cases, it kind of went all over the place.

So just -- just a snapshot and an example of how these can change over time. Go onto the next slide.

Okay. So we'll briefly go through hearing assessment in the pediatric population. I know some people touched on the ABR, the BAER. But on the next slide, I want to kind of break these things down in between a, quote/unquote, "objective hearing

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assessment and subjective."

So more objective hearing assessments that we do in audiology, otoacoustic -- otoacoustic emissions is one particular test. It's often what you see in newborn hearing screenings. But you can actually do a more diagnostic test too where you can look at frequency-specific responses.

And these are responses reported from the inner ear. They are typically represented of outer-hair cell functions, so you aren't necessarily capturing inner-hair cell functions. We don't need to get into that distinction for this talk.

But it has its limitations in terms of interpretation. But it can indicate some degree of hearing loss, and that's why we use it when we screen.

The gold standard, I think, for right now at least in the little ones -- in the neonates, is auditory brain stem response I'm sure most of you are familiar with. You put stickers on their forehead, behind their ears, and you can record the auditory nerve response to sound, and you can get an estimate of the child's hearing loss.

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These are also used as screening tools, especially after the initial screening has failed. But they can be diagnostic. You can look at frequency specific ABRs. They can get tricky, as we'll talk about, as kids get older, and they start to get squiggly.

So if you go to the next slide, behavior assessment -- here, I guess I said, "subjective." But really, I like to think of that as behavioral hearing assessment in children.

The next step after the ABR, if you're able to get some behavioral information, is visual reinforcement audiometry. This is often used for children from 6 months to 2 years of age.

It can be difficult to get an ABR on a 6-month-old, you know, unless they're just fast asleep and they don't move for a while.

And in this case, often the child sits in the parent's lap, and they're kind of directed toward -- toward the midline. And then you have speakers on either side that present a sound, and the child turns their head, and that's how you know they

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heard the sound.

It's pretty neat, and it's pretty effective. But you often are doing it in the sound field and locate your specific information that way. So you would only have kind of a sense on how the better ear is doing, for the most part.

There's also condition or play audiometry, which is kind of moving toward the adult audiometry. Between 2 and 5 years of age, they -- they play a listening game, like putting a block in the bucket when they heard the sound or sometimes hitting a button that lights up.

In some cases, especially as they get older, you can put in headphones and you can get some ear-specific information, and then finally, you can move them to -- congenital -- conventional audiometry in children 5 and older.

I've been able to do it with some precocious 4-year-olds. But this is your classic hearing test where they raise their hand when they hear a sound, and they push a button, or you can get them to say something that -- that, you know, excites

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them, like, "I hear it," or something else.

And you can get a conventional audiogram -- maybe not all the frequencies you want. But you can move in that direction. Okay. So next slide.

So this is just from the review paper. I know other people here have -- have talked about some of their protocols at their centers that they use for assessing hearing loss in CMV. So this is by no means meant to represent all -- all approaches. But it's something to think about as we get into thinking about the study design.

So at -- at the centers that they looked at, children were diagnosed with hearing loss after undergoing otomicroscopy, tympanometry, reflex threshold measurements, behavioral audiometry if they're able to get that, of course; they have to be a little older.

Click-evoked ABRs and tone-burst evoked ABRs, those are just two different types of stimuli. We don't need to get into that here, but, you know, two types of ABRs.

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And they are doing these measurements when possible every three months for that first year, ever six months until they're 3, and then every year after that up to 6 years of age, and then they likely move into our classic audiometric care if they're stable.

So that's just something to kind of think about, how often they are measuring this hearing as you think about study development, because it's -- it's quite a lot, and it changes over time, as does their ability to perform these hearing tests. All right. Next slide.

Okay. Now we can get into what everyone wants to hear. I know I moved through that kind of fast. I hope that -- that most of that was pretty basic for you all.

So if you go to the next slide -- okay. So I kind of have some general considerations here, and then I know that people are interested in talking about end points and how to time end points. That came up yesterday in the panel discussion, and we certainly talk about it again here.

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But when I was putting this together, I was thinking about how I could -- you know, how frustrating it is. But I -- I can't give you, you know, one perfect answer. But I -- I think there are some things you can think about as these things are developed.

And one of them, of course, it sounds obvious, but I think is really important, is to consider your treatment and study goals.

So I heard a lot yesterday in the discussions about preventing or stopping progression of hearing loss, which, of course, is -- you know, would be the goal; right?

If they don't have to have severe hearing loss in the first place, that's obviously the ideal situation. But there are a lot of challenges with that for many reasons.

So, you know, depending on what you're trying to do in your study, you may be looking at preventing progression of hearing loss, maybe improving existing hearing loss, or even trying to just stabilize existing thresholds.

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So that could kind of lead into these other two goals here. But maybe you want to show that you can produce fluctuations in hearing loss with these -- with a drug, let's say.

So that's something to think about, because it will inform your end points, and it might even inform the timing of your end points and the kind of data you're going to collect.

So the next bit, I don't want to perseverate on, because other people have talked about it in the ethics talk and in the rear-world evidence discussions and elsewhere.

But of course, a comparator group might impact -- well, it definitely will impact how you structure your end points or structure your study design. You know, you may consider comparing interventions to standard of care.

And I'm just talking about hearing loss here, keep in mind. So I'm -- I'm on this narrow focus.

I don't want to get too much into the real-world evidence world. But, you know, there may

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be centers that you're at, potentially, that have available audiometric information for comparison in -- in other populations or if there were -- other children had diagnostic ABRs for whatever reason. There may be some sort of comparator group.

But these two things at a high level will inform how you develop your end points, of course. So on the next slide -- okay. So there's a lot here, and we can get into it in the panel. But I just want to kind of briefly go through it.

So there's kind of three big areas here that I thought about when thinking about developing audiological end points -- of course, a big piece of the demographics of your targeted population in any study you're developing.

So I know we've talked a lot about, you know, early diagnosis and -- and kind of the -- the critical period after birth for stabilizing children that have a myriad of potential issues with CMV.

But in terms of hearing loss, I'm thinking about what age are they diagnosed with the CMV, especially if, you know, it's asymptomatic and --

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and something emerges later. When were they diagnosed with the hearing loss? That could vary depending on any number of factors.

So depending on what you're kind of trying to do in your -- in your clinical trial or with a drug or some kind of treatment, you know, there might be differences among the population you're looking at in -- in terms of when they were diagnosed.

Age at hearing loss assessment will impact the testing approach. So I touched on the different testing approaches, the type of data you can generate, you know, whether you are able to get an ABR on a, you know -- I don't know, 1-year-old -- maybe not.

So you might be looking at something, you know, less ear-specific information. You might be looking at sedated ABRs, and maybe that's okay. But it can complicate the kind of data you're generating in terms of hearing status.

And -- and also, keep in mind that some children, especially as they get older, might be using amplification, like hearing aids or even cochlear

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implants in one or both ears.

So, you know, that -- that doesn't preclude you potentially from doing a treatment or measuring their hearing. But it could actually introduce some opportunities for showing some -- some functional improvement, hopefully, after some sort of treatment, and we'll talk about that a little bit more. But this is a heterogeneous group in a lot of ways, or it can be.

So test conditions for primary end points, so of course, the test conditions -- audiologic test conditions should reflect your study goals. If you're looking at preventing a hearing loss, you might structure your end point differently than if you're looking at stabilizing hearing loss, et cetera.

Man, I wish I had an answer for you -- for you on this one. We talked about it a lot in our group. And there's just no perfect answer. But traditionally, in some cochlear implant studies, people would often focus on the worst -- quote/unquote, "worst ear" to show, you know, a

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maximal benefit with cochlear implantation.

And that approach can be taken I think in other -- other types of studies where you have a worse ear. You're looking at the maximal benefit from treatment. You're kind of, quote/unquote, "potentially getting that ear back" or "getting less hearing loss."

But I think other people brought this up yesterday, and that's a good point that if -- if you have someone with asymmetrical hearing loss, they have a bad ear and a good ear. But they still have hearing loss.

If the worse ear doesn't get any better, that doesn't mean that the better ear can't benefit from some kind of treatment. So you may want to focus on the better ear, depending on your study goal or even both ears, you know, if your goal is hearing loss prevention.

It's kind of -- you know, it can be difficult to prove a negative. But depending on what the hearing loss looks, like, you don't want to throw out the baby with the bathwater, I guess -- throw out

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one ear that did benefit, and just focus on, you know, the poorer ear, if you -- if you think your treatment might benefit both.

So you really need to think about that and let your study conditions reflect that, because I don't think there's necessarily a wrong answer or right answer here. But it needs to kind of tell the story that you're study is trying to tell.

And as I mentioned, demonstrating benefit through measuring functional outcomes is something that we see a lot in CDRH and in other -- other types of studies that -- that measure hearing loss, frankly, in the drug arena as well.

But if people -- if children are coming to you, let's say, slightly older, they have hearing aids fitted. They have hearing loss. You want to get them fit as soon as possible.

We do see people measure audiometric improvement in what we call "aided conditions." So if you want to see what their hearing sensitivity is like, you would take off their hearing aids; you would test them.

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But you can also show potentially that maybe improved underlying hearing is also improving some of their functional outcomes with their devices, which is also a great thing. You don't have to have normal hearing to have, you know, great functional outcomes.

We also look at measuring speech discrimination in these conditions. So you give them word lists. You show that they're, you know, able to get more words right or even sentences as they get older.

And there are also, for younger children, parental questionnaires. There's something called ITmaze. You can work with parents to talk through different aspects of their child's auditory kind of awareness and sound awareness and interactions like that as they get older even. And that will also help inform some functionality.

So I think that's something to consider as well. The audiogram is one piece of the puzzle that's showing that it actually is translating into something meaningful for these children -- I think is

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also an approach you can take. All right. Next slide. I think I'm almost done.

Okay. So getting into time point considerations, this is another thing I wish I could answer for you. But I can't. It depends on your study. But I kind of broke it down into two pieces that I think are worth thinking about. And I think people have touched on this before and how tricky it is.

So there's kind of this short-term assessment of hearing status post some kind of intervention. Obviously, the frequency of your hearing evaluation and your time points are going to vary depending on your treatment.

Whatever your treatment is designed to do, you may want to measure hearing every month, every two months, every six months. It -- it just depends on your approach.

Obviously, children are going to be younger for these evaluations, if you're enrolling little babies in these studies. So that, of course, impacts the data you can collect. You might be

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collecting ABR data. You may, you know, hit a point in your study where you can get some behavioral data. But it's not useful to you.

You have to kind of think about that. How are they going to age in sort of the short-term of your study and then long-term assessment, of course, of hearing and even language post intervention.

So you might want to assess stability of hearing status over time. This can pose difficulties, as discussed, due to the nature of the CMV-related hearing loss. So it can fluctuate, obviously, on its own.

It can normalize in some cases and never fluctuate again. It can get worse and never fluctuate again. So it is tricky. But that is something that -- that would be worthy of assessment in the long-term and then even language development in relation to hearing status.

So getting back to those functional outcomes, as children get older, they can be tested by speech pathologists and shown that, you know, they still have hearing loss; but their hearing has

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improved; their functional outcomes have improved, and their language development is on par with their normal hearing peers, let's say. So that's another potential approach long-term.

So to move into, like, you know, FDA speed, I kind of think of this as a pre- to post-market balance when developing time points for studies. Maybe propose a time point for your pre-market application end point.

You're coming into us with a study; you want to get a drug approved up to a certain age, and then maybe there's a continued follow-up in the post-approval study space.

And of course, these -- whether this approach is viable is going to depend on your study design, the proposed indications for use, your intended population, marketing claims, those things.

But it could be one way to sort of capture these two time points without having to delay innovation on -- on the drug development side too much. All right. Next slide.

I'm going to fly past this one. I

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don't know if I needed it. But I was kind of thinking about developing a road map when you look at -- at these studies, clearly defining your treatment and your groups, carefully considering your intended treatment population and the kind of data you can generate when developing your end points, considering short- and long-term assessment, looking at longer term stability of the hearing status.

And then depending on your study, design and intervention, you may be able to consider a pre- to post-market balance and how you're developing your study and proposing your end points.

And then my last slide here. So as I've been reiterating, hearing loss in children with congenital CMV is very often a moving target.

This hearing assessment in children changes with age, which can change the type of obtainable audiometric information, also a moving target as you're study goes on.

And these factors are going to impact how you develop your end points. And you have to keep that in mind as you're developing the study -- kind

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of, you know, the moving target of both their age and development and the hearing loss.

And one recommendation -- I'm not in CDRH -- but we have a similar process in CDRH, you could use the pre-IND process to come in and discuss your proposed -- proposed protocol with FDA, which can help guide you further before you kind of dive into the -- the IND study process. And, you know, I would leave that to CDRH.

But, you know, there's certainly mechanisms for coming in and -- and kind of proposing what you want to do. And, you know, FDA has the same goal as you to help these kids with hearing loss so would work with you on developing a protocol as well.

And I think that is my last slide.

DR. HODOWANEC: Well, thank you, so much, Dr. DeVries. We really appreciate you sharing your audiology perspective on these various assessments and end-point considerations. Very -- very helpful.

And yes, in CDRH, we fully endorse the use of the pre-IND program as well. It can be very

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helpful to discuss some of these questions early on in -- in a development program.

I will now introduce Dr. Ryan Kau. Dr. Kau is a medical officer in the Division of Health Technology in the ENT Device Team within the Office of Health Technology 1, Office of Product Evaluation and Quality in the Center for Devices and Radiologic Health at FDA.

Dr. Kau's presentation is entitled "Alternative Routes of Drug Administration." So thank you, Ryan. We're excited to hear about this novel consideration.

DR. KAU: Okay. Thanks -- thanks, Aimee. So today, I'm going to talk about specifically one alternative route, which is the transtympanic injection, and I want to provide an overview.

And it's potentially used as a valid administration for hearing loss indications and specifically to this talk, congenital CMV hearing loss. Next slide, please.

So I'm going to go over the history of transtympanic injection, the procedure itself, the

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anatomy of the cochlea, potential complications, and advantages of this route of administration, and specific considerations for the targeted population of congenital CMV hearing loss patients. Next slide, please.

So transtympanic -- transtympanic injections have been used as far back as the 1950s, in which aminoglycosides were used to treat vertigo. Currently, corticosteroids and aminoglycosides are two commonly utilized drug classes administered transtympanically for off-label uses.

Corticosteroids are used for sudden hearing loss, Meniere's disease, autoimmune inner ear disease, and aminoglycosides are still being used for -- for those, specifically with Meniere's disease. Next slide, please.

So the procedure itself, typically, it's -- this is done in the office. This is mainly done in adults, for the most part, currently. And it's usually done with otomicroscopy.

Patients are placed in the supine position, and then the physician has the option to

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anesthetize the tympanic membrane site of injection. Delivery of the drug is then made through the TM, and basically, this is done through the needle perforating the TM and then injecting it into the middle-ear space.

There is an option of placing a second hole to relieve pressure when injecting. And there's also another option of whether we would want to put a tympanostomy tube prior to injection, especially in patients where we are going to be providing current treatments.

So after this is done, the patient will remain in the supine position, and the ear that was treated will be turned away from the ground. And typically, this is the position they will hold for the next 10 to -- to 30 minutes.

The patient is told to refrain from chewing or attempting to pop their ears or yawning, because we don't want the medication to drain from the Eustachian tube. Next slide, please.

So this slide, you can see a needle going through the TM into the middle-ear space. And

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as you can see, the Eustachian tube is connected to the middle ear and, therefore, allows for a drainage path of the drug into the nasopharynx.

The picture here is somewhat misleading in that we would use a -- typically, use an ear speculum and along with usually a spider -- a spinal needle, which is longer than what this seems, like, here.

But you can see that it does show you where the round window is in the cochlea, as well as the ossicular chain and the Eustachian tube.

And oftentimes, when we inject, we are aiming towards the round-window membrane, because that is where we would want the drug to enter into the cochlea. Next slide, please.

So the cochlea has three main fluid chambers -- just some basic anatomy, the scala tympani, the scala vestibuli, and the scala media. The scala tympani and the scala of vestibuli contain perilymph fluid, and they communicate at the apex at the helicotrema.

And the scala tympani contains the

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endolymph fluid. Of note, the scala tympani is the space that is attached to the round window, and of also note is that there is a blood-labyrinthine barrier, which is a barrier between the vasculature and the inner ear fluids, and this has been noted to be an obstacle in delivery of system drugs to the inner ear.

So this can be a problem when giving systemic drugs to affect hearing -- hearing loss for hearing loss indication.

Also note, in the lower diagram, there is the inner and outer hair cells and the inner -- inner hair cells and outer hair cells are potential products for drug products to treat hearing loss since damage to these sites is often thought to be the etiology of some hearing loss.

So whether a transtympanic route of administration would be beneficial for an indication would depend on the exact path of physiology of the -- of the hearing loss.

And so if a injury to the hearing function is thought to be occurring at the level of

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the inner ear, the -- there's a potential for benefit with this route of administration. Next slide, please.

So this is a list of potential complications. By far, the ear pain and ear fullness are the most common adverse events, along with dizziness and headache. And these are typically transient.

Persistent TM perforation can occur with any type of procedure where you're perforating the TM, and therefore, frequent injections and extended durations of these injections can increase the risk of persistent TM perforations. Next slide, please.

So some potential advantages -- so the advantages of transtympanic administration are basically consistent with advantage of any type of local drug delivery to a target location, and in this case, it's the inner ear.

It can allow for a lower dose and a higher local concentration of the drug. And this has been seen specifically with use of corticosteroids.

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The other advantages listed here can contribute to the ability to have lower dose and higher concentration of the drug. The -- the -- this transtympanic administration avoids systemic side effects of the drug, as well as first-pass effect.

And in addition, it bypasses the blood labyrinthine barrier. And overall, it could decrease the systemic side effects and would allow for longer duration of administration if needed. Next slide, please.

So what kind of considerations should we think about for this congenital CMV hearing loss population? I think the -- the biggest one is going to be tolerability, obviously.

I think since the congenital CMV hearing loss population would be quite young, it's whether this patient population would be able to tolerate this type of administration.

For example, you know, we would consider whether -- whether transtympanic injection would require going to the operating room and requiring anesthesia or if this could be done

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inoperative procedure.

I think if it would require recurrent anesthesia, I think that would be not ideal and likely would outweigh the benefits of the local administration.

The patients could tolerate an inoperative procedure. The viability of transtympanic administration in congenital CMV hearing loss would then depend on dose frequency and dose duration expected for the drug.

If there will be frequent dosing, perhaps it would be more tolerable to actually place a tympanostomy tube in the -- in the TM. If it's less frequent or of a short duration, perhaps patients could tolerate the -- an infrequent office injection.

And also, less frequent dosing may -- to -- to have less frequent dosing, you may require the ability to have a longer drug exposure in the middle-ear space to the round window.

This could be done by formulating a drug that would stay in the middle-ear space better than perhaps just a -- better than just a solution.

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An excipient, such as a poloxamer or 407, which has been studied for its real pectic properties, is an example of this. And where the liquid is -- where it's liquid at room temperature, but then becomes more viscous at body temperature. Next slide, please.

So in some rate, transtympanic injection has many established advantages for drug delivery to the cochlea. Whether this would be a potential use for patients with congenital CMV would be based on weighing the advantages and disadvantages of this route of administration with specific considerations to tolerability in this younger targeted population. Thank you.

DR. HODOWANEC: Thank you, very much, Dr. Kau. Very interesting. Some -- some food for thought for all of us.

We will now welcome Dr. Megan Pesch back to our virtual podium. Dr. Pesch will be switching hats and will now discuss neurodevelopmental outcomes in children with congenital CMV, a wide spectrum.

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Welcome back, Dr. Pesch. Thank you.

DR. PESCH: -- so much. All right. Let's get into it. Next slide, please. Next slide.

All right. So today, we'll talk briefly about why congenital CMV can cause these developmental differences, who is at highest risk of developing delays and disabilities, specific areas of disability delay and differences, patterns we see in kiddos with congenital CMV, as well as treatment, management, and support.

And this will be a very brief overview of a giant topic. Next slide, please.

So why do we care about congenital CMV? I probably don't have to tell you, because you all have been here all day. It's a leading nongenetic cause of neonatal and childhood hearing loss, and today, we're really going to focus on the risk of other neurodevelopmental delays. Next slide.

So as we heard earlier this morning, the pathophysiology of congenital CMV in terms of severity, the earlier the virus is transmitted to the growing fetus, the greater risk of severity of the

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sequelae there is.

And that runs kind of in opposite direction of transmission, which we know increases over the course of gestation, so higher risk of transmission, lower risk of severity of sequelae with later -- later transmission in the gestation. Next slide, please.

So this is just a very brief overview. But I like to think of the mechanisms of fetal injury, because it really helps me then think about the sequelae and how those are caused.

So there are three main mechanisms -- and this is a simple way of looking at it, but three main mechanisms of injury to the fetus.

One is that placental injury. CMV can get into the placenta, into the villi, into that fetal maternal interface, cause inflammation, vasculitis, and in turn, can decrease blood flow to the fetus, which can cause end organ damage or even just those smaller babies that we can see with congenital CMV.

CMV also loves fetal CNS cells. And as someone mentioned earlier today, the reason for

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that -- loving the fetal CNS versus and adult or even, like, postnatal CNS is -- is unknown. But getting into those fetal CNS cells, especially early in that first trimester, can have a giant impact, especially on early brain development.

And then everything -- I like to think of development, you know, everything downstream from that. If those early foundational structures of the fetal brain are not formed correctly, then additional structures, you know, it kind of -- it's almost, like, a logarithmic effect.

And then, of course, there's the maternal immune response. Some maternal immune response is good. But some -- or -- but a lot can be too much.

And of course, that maternal immune system is kicking in, revving up, throwing out cytokines, throwing out antibodies. But that, in itself, while they're attacking the CMV within the fetal cells, can disrupt that fetal cell replication and even apoptosis.

So those are kind of the three main

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areas that we see in terms of the mechanisms of fetal injury. Next slide, please.

So it's no wonder that we see a lot of CNS related neurodevelopmental sequelae in these kiddos. The one exception, I would say, would be the ear, so the hearing loss and vestibular disorders. I guess it's arguable. They're, like, CNS adjacent; right?

So depending how you look at it or where you draw that line. But thinking about that early invasion of the fetal brain, that inflammation, perhaps decreased maternal blood flow through that placenta, you -- we can see motor-planning disorders.

CMV tends to really love the vasculature around the basal ganglia. So even we can see more severe motor-planning disorders, like cerebral palsy, but then also some less severe ones -- the softer signs that I'll talk about in just a little bit.

We can see more profound intellectual disabilities, slight learning differences or disabilities, certainly epilepsy. We see the visual

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loss and impairment, which again is from the chorioretinitis, which was discussed earlier -- also see autism.

I put a star there, because this a point of some controversy in the literature. Although, in my mind, it really isn't controversial. These kids are just coming out of the woodwork in terms of what we see clinically. Next slide, please.

So I won't belabor this point. We've put these kids into two buckets for so long; right? But we all know it's such a complex disease process. The two buckets just really don't suffice.

And, you know, classically, we thought that it was the kids that were born symptomatic -- that 10 percent, that are the highest risk of sequelae, which is -- is still certainly true.

But the kiddos that are asymptomatic, you know, aren't completely home free, so to speak. They are still at risk of sequelae. Next slide, please.

And again, I'm a simple person, just -- so think of this in kind of a simple way. Symptomatic

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babies are -- have signs at birth. Many do have SNA -- or sorry, sensorineural hearing loss, and most go on to have a typical development. And then it's vice versa for the asymptomatic kiddos.

"Clinically inapparent" is another way that we've discussed describing these kiddos. And I think that's just a lovely way to say it. Although, they may too have sensorineural hearing loss, and most do go on to have typical development.

And I -- I kind of put these "typical" and "atypical" in air quotes or quotes, which I -- I tend to love and use a lot in my vernacular.

But I really think that we -- some of these studies that are going on right now -- these lovely longitudinal studies that are really robust when following these kids longer will give us some more definitive answers about the development.

But there are so many holes in the literature that I'm hopeful that most kids with asymptomatic CMV do have stone-cold typical development. But I'm kind of -- I'm a little hesitant to say that with full confidence, just from what I see

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in my biased clinical experience. Next slide, please.

And then if you could just click forward. I think there's -- there we go. So again, the -- but in general, we see the severity of sequelae increasing with the severity of disease.

And I just put some of the other names here that we refer to, the clinically inapparent, apparent, CMV disease, CMV infections, and genetic asymptomatic. Next slide, please. Oh, there you are. Thank you.

But this is something that the studies haven't really looked at so far. And it just seems so obvious to me as a developmentalist. But other factors that are really -- that impact long-term developmental outcomes for any kiddo; right?

Maternal education, there have been a couple studies that have controls for that. But what about access to therapies or access to healthcare. Some studies do control certain gestational age, but not nearly enough.

Singleton versus multiple pregnancies, socioeconomic status, social determinants of health,

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all of these things go into, you know, any child's development and prognosis and what they have access to.

So I think important to keep these in mind as we think about these kiddos who, you know, are born how they're born. And while we're doing so much to try to prevent CMV, you know, kind of when these kiddos are born, you get what you get.

So what can we do to optimize these long-term outcomes? And I think even beyond the antivirals, we need more answers for these families. Because after six months, kind of then what?

And, you know, we don't have great answers to that, at least that are backed by data. Next slide, please.

I am just going to say that one of the theories around CMV and hearing loss is that it seems to be drawn to the microvasculature of the inner ear. But that's just one of the hypotheses. Next slide.

I'm going to skip over this. We just had a lovely presentation earlier about CMV and hearing loss, so I think CMV and hearing loss, it's a

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thing.

These are -- I was looking at this slide this morning, and I think it's a touch misleading. So if you could just pay attention to what I'm saying, so I can explain this.

So when we think about these kiddos with asymptomatic CMV and long-term outcome, so the longer you follow these kids in cohorts, the more -- the higher the percentage that develop hearing loss. So a lot of the cohorts say, you know, 10, 15 percent by, like, you know, 4 or 5 years. But that's only in the four and five years.

The couple of studies that have followed kids even longer, over decades, have shown percentages kind of higher, like, 15 to 20 percent. This is the stat that I think is a little misleading.

In some studies of asymptomatic children -- so this is not allcomers, but in -- within the cohort, 45 percent have had gaze and vestibular dysfunction, and then 30 percent within these cohorts have had balance difficulties.

So whether or not that can be

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generalized to allcomers, I don't think that's really known yet. But to say that these are significant things that can impact kiddos with congenital CMV, even those that are clinically inapparent. Next slide, please.

So just briefly, I wanted to mention that I think we're learning more and more how important longitudinal follow-up is for these kiddos, maybe even into the teen years; and that congenital CMV is -- is an indication for unilateral cochlear implantation sometimes for other conditions.

Especially associated with unilateral loss, it can be a little bit harder to insurance hands to cover it.

I also say that cochlear implant outcomes really vary for kids with CMV. And the literature supports that. It seems to really depend on other sequelae, of course.

And so it's -- it's really tough, because you've got this little baby, perhaps with some soft brain abnormalities -- definitely with hearing loss.

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And I think often my colleagues in otolaryngology, you know, just look at a kiddo with sensorineural hearing loss and, of course, hope -- hope for the best in terms of language outcomes.

But I think with these kiddos with CMV, there can be so many soft things that interfere with language acquisition that really, from the get-go -- and this is my personal belief, that they need multi-modal communication, so sign language, as well as access to oral spoken language for CI recipients, because it doesn't always go kind of in that textbook way. Next slide, please.

So briefly, just on the motor delays and disabilities, a lot of these kids are floppy. They just have this really low tone and slow attainment of those motor milestones. Most of them get there, which is great, but not walking until 18 months, 24 months.

And I'm not talking about the folks with cerebral palsy, but even those asymptomatic kids, something we see clinically.

And then the poor coordination goes

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along with kind of having that low tone, low muscle strength, or slower to develop, as well as vestibular dysfunction. Next slide, please.

Feeding disorders are something that we see pretty frequently, and it seems to be -- and this is more anecdotal, because it really is understudied.

If you're -- if you get on the CMV Mommies Facebook site, it -- it blows up when you talk about feeding disorders and difficulties.

There's a lot of differences in how these kids seem to process textures or tolerate different textures. There's also the coordination of chewing and swallowing.

And of course, this make sense for a child who may have cerebral palsy or something more, like a diagnosis of muscle and brain communication differences.

But there has also been some theories about chewing and swallowing difficulties, perhaps in these kids being associated with hearing loss and the kiddos with profound hearing loss, not using those muscles quite in the same way and having somewhat of a

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slower gain in those skills.

Again, it's just a theory. For these kids, we do swallow studies, feeding therapy, occupational therapy. Next slide.

Communication disorders certainly associated with hearing loss, coordination of the muscles of the mouth can be challenging for a lot of kiddos. I also think there is some layers here with autism and social communication differences.

And it is exceptionally tricky when you get these kiddos with autism and hearing loss and trying to kind of decipher what -- what comes from what, which again is why I'm a strong believer in multi-modal communication for these kids as early as possible.

And then you peel back what they don't need and what they don't, you know, gravitate towards as they grow up and kind of declare it themselves. Next slide, please.

So autism, we have a paper coming out, Dr. Lanzieri and I and the -- the group from the CDC coming out later this month, which support -- which

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shows a 2.6 times increased risk of congenital -- or sorry, autism with kiddos with congenital CMV.

Several studies have found this, many in -- in small cohorts and anecdotally. I think just it makes sense, because from what we know about autism, you know, the epigenetics of it and also just really for anyone who is a pediatrician or who has worked with young kiddos.

Any disorder that causes perhaps a malperfusion of the placenta or risk of brain injury, we always see, you know, prior risk of autism, just in general in those populations. So it makes sense why CMV would be -- would increase the risk as well.

I think in these kids it's tricky; right? Because it takes a while for the autism to kind of come forth. And so they may need different approaches to therapies and communication as well.

Early intervention is always critical for any of these delays. I think all kids with congenital CMV should be eligible for early intervention monitoring.

With autism in particular, knowing the

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higher risk, and these kiddos need support and not -- I would say, cures, because we're not looking necessarily to cure autism, but to help these kiddos, you know, have -- lower their challenges, work on their strengths, increase their social communication in ways that are comfortable and true to themselves.

And I also think -- I just wanted to mention, there's this fascinating overlap between autistic and deaf communities. The deaf community is really one that had taken on this rejected -- this disability identity thing. You know, "We are deaf -- big D, Deaf. We're proud. We're not broken."

And we're seeing that now within the autism community as well with the neurodiversity movement. Next slide, please.

There's also a increase in behavioral disorders and challenges. We see externalizing behaviors that -- like, kind of the aggression, outward oppositional internalizing behaviors or more that anxiety, depression.

A lot of impulsivity in these kiddos, even the asymptomatic kiddos. And then, of course,

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this is all compounded by any sort of communication or movement difficulties or sensory seeking tendencies. It can be really tricky to disentangle all of this. Next slide, please.

So really, I think this is what we should be moving towards or -- or some version of this.

You know, we see these kiddos and how they are born. They're born symptomatic or clinically apparent or, you know, whatever you call it, and then asymptomatic, how they look at birth, but then their functionality, how they develop over time is influenced by a myriad of things and not just their status at birth.

So I think kind of using this spectrum -- you know, I'm a developmental pediatrician, so I love the spectrum.

And, you know, I think this is kind of more where we should be moving and thinking of these kids' functional status, over time moving from this, like, binary simplified how they were born at birth predicts their forever outcomes. Next slide.

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And I'll end there. Thank you.

DR. HODOWANEC: Wonderful. Thank you, so much, Dr. Pesch. I would now like to introduce our last speaker for Session 2, Dr. Rachel Greenberg, Associate Professor of Pediatrics in the Division of Neonatology at Duke University School of Medicine and the Duke Clinical Research Institute.

Dr. Greenberg will discuss clinical "CMV drug development: Where do we go from here? Experience of the Pediatrics Trials Network." Thank you, so much, Dr. Greenberg.

DR. GREENBERG: Thank you, so much. My name is Rachel Greenburg, and I'm a clinical researcher, and I'm chair of the steering committee for the Pediatric Trials Network.

And I'm also a pediatrician, and my clinical work is as a neonatologist taking care of infant -- virtual connectivity interruption -- and so the NICHD and through the legislation provided by the Best Pharmaceuticals for Children Act has sponsored the PTN to improve dosing, safety information, and labeling.

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And the focus of PTN's work is primarily on off-patent therapeutics, so medications that have been used for a long time and are no longer on patent, and there's not -- there's not a lot of interest in -- in studying them outside of the -- the sponsoring through the NICHD and the PTN. The next slide, please.

So here's the typical schematic that shows the big picture of the very long and complex process of drug development, and, you know, we've -- if you've been in the space in the past, you've probably heard that new drugs can take 10 to 15 years to come to market.

And so the role of PTN is we're coming in after all of this -- after a drug has come to market. But often, the oldest drugs were not -- were not studied in children, but where clinicians are forced to use some medications, and so we have to use them without all of the safety and efficacy data that would -- and dosing information that would have been beneficial to guide us.

So PTN comes in after all this is done,

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works with the FDA to -- to have a plan to -- to perform the studies -- often phase 1 or pharmacokinetic studies, phase 2, or safety studies, and working with the FDA to review these data and hopefully make changes to that drug label to reflect what is that new data for safety and efficacy and dosing. Next slide, please.

So this is a sort of outline of what PTN's pathway to changing a drug label looks like. So as I mentioned, the NIH collaborates with the FDA, and they establish a list of priority molecules that are being used without -- without effective data -- data on safety or efficacy. And they sponsor pediatric trials.

And the Pediatric Trials Network does these. And Pediatric Trials Network consists of a clinical coordinating center at Duke and a data coordinating center at EMIS, and we connect those studies in areas that are identified on the priority list, either the medications or the therapeutic areas that are of priority.

And then those study data are submitted

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to the FDA for review and consideration for possible changes to those drug labels. Next slide.

So there -- there are a ton of folks involved in doing the studies that may have made this effort successful. And including sites and participants enrolled from all across the country, this just shows those dark purple areas are -- are places where children -- participants have been enrolled in PTN studies.

The light purple areas are areas where we're expanding into at this moment, and so really have covered the country in terms of places that were able to conduct studies to find this important information. Next slide, please.

And this is the latest infographic just to show the accomplishments of the -- of the PTN in terms of what we've been able to find out in this space. So we've enrolled over 12,500 participants, and you can see the little icon there representing the therapeutic areas that we study.

We're really agnostic to therapeutic area, meaning, you know, we will study anything from,

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you know, menial intensive care to cardiology to pulmonology to infectious disease to psychiatry, anywhere there is a deficiency in data.

And the studies that we've done have led to this -- this infographic is out of date as of just last week, it's now up to 21 changes to medication labels that we've affected as a result of this effort. Next slide.

So these are the molecules for which we have either done the studies to support the data and submitted the data CASIA to change the label to add pediatric information.

And we're just missing here oxycodone, which is the most recent one. That was our first molecule for which we added information with -- in collaboration with the -- with the FDA and the -- the NDA holders to the -- to the label for oxycodone in the lactation space.

So prior to that, there was no -- really, very little information in the drug label on how the drug was passed into breast milk, and now that information is there.

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The one -- the label change that occurred prior to oxycodone was fluconazole. And because it's in that infectious disease space as well, I thought I'd give that example just to illustrate, you know, what we -- what -- what motivates us to do these types of studies and, you know, how that might be applied in the CMV space. Next slide.

So for -- in the fluconazole label before the -- the PTN studies, the old label contained almost no information related to how to use this drug in infants, even though it was commonly used in the clinical setting to treat Candida or yeast infections.

If you could go back, please. So those infections are -- thank you, they're often fatal in infants, and they cause long-lasting health problems for infants that survive.

So the label change was a result of four studies, multiple analyses that were supported by PTN, and much -- and negotiation with the FDA in terms of how to incorporate that information.

And now the new label contains information on pharmacokinetics and dosing

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suggestions, including the use of a loading dose, as well as information on the use of fluconazole for both treatment and for prophylaxis or prevention of Candida infections in full-term and premature infants.

And we also added information for pediatric patients on ECMO. So that's newly included in the label as well.

So that's just an example of the type of work that -- that we do. And, you know, that -- that label -- that FDA label provides the guidance that then trickles down to -- to guidelines and everything that clinicians use to treat patients. The next slide.

So the PTN is -- is -- absolutely has been interested in infants for quite some time. So infants, particularly hospitalized infants, but also infants in the outpatient setting are -- are frequently prescribed medications off label.

We did a study looking at the top 50 medications used in infants with extremely low birth weight, so born at less than 1,000 grams, and only 20 of those top 50 or 40 percent were FDA labeled for use

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in this population.

So as part of a way to try to deal with the magnitude of this problem, we tried -- we wanted to create -- we had this idea of creating a master protocol for hospitalized infants that could be used to study multiple diseases and medications under a single study.

And so then we were looking for particular disease areas and focuses that would be high yield in terms of where the need was. The next slide.

So in terms of disease processes and therapeutics of interest in the infant population, CMV was absolutely high on our list.

So as the -- you've heard today, most clinicians use ganciclovir or valganciclovir to treat congenital CMV that is symptomatic, recognizing that as we heard from the last speaker, there are many categories of -- of symptomatic in many buckets.

But we -- just for -- for simplicity's sake at this point, ganciclovir and valganciclovir are used to prevent those outcomes that we don't want to

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happen, so hearing loss and neurodevelopmental impairment. And the use of these drugs is based on existing data and consensus guidelines. Next slide.

But the priority list of molecules developed under the Best Pharmaceuticals for Children Act includes infections and neonates as an area of therapeutic need where there is -- you know, there are quite a number of infections, including CMV, for which there is actually not a molecule available, not -- not a medicine available, according to drug labels that are -- that are approved to treat these infections.

So ganciclovir and valganciclovir are included within this area of infections as drugs for which label updates are needed. And so, you know, at this point, clinicians are using these medications according to consensus guidelines and according to standard of care, but without FDA guidance, because that information is not in the drug label.

And you can see this is a study we did looking at a large healthcare database, looking at infants hospitalized in NICUs all across the country, and on -- on the right graph there, you can see on the

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Vioxx is the proportion of infants.
These are infants with -- diagnosed with congenital CMV who are treated with either valganciclovir and ganciclovir during their hospitalization in the NICU. And this is a NICU population.
And then on the X axis, you can see over time that treatment for congenital CMV has increased over time to the point -- in the most recent data that we had at the time, over 75 percent of infants with congenital CMV in the NICU are being treated with valganciclovir or ganciclovir.
And we actually didn't have data on symptomatic -- of symptoms of CMV, so it's -- it's likely that many of the untreated infants were -- were asymptomatic in this population. Next slide.
So what is the evidence base for treatment and why isn't this information in the -- the labels for these medications at this point?
So we've -- we've heard previously today about some of these landmarks that even -- thanks to Dr. Kimberlin and his colleagues for -- for

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doing these, you know, hugely important studies in this space and, you know, being persistent over time to try to establish what we can do for infants with congenital CMV.
So the first -- the 2003 study compared six weeks of ganciclovir versus placebo and showed prevention of hearing deterioration at six months of age.
And the second study compared 6 months versus 6 weeks of treatment and showing that longer treatment did not have significant benefit at 6 months, but showed improved hearing outcomes at 12 and 24 months, as well as improved neurodevelopmental scores. Next slide, please.
So that seems, like, pretty compelling data, and those data are the basis for which clinicians are using ganciclovir and valganciclovir to treat infants with congenital CMV. But both of these studies had, you know, some issue that have led regulatory bodies to think that more data are needed.
So for the first study, although it was pretty compelling data, only 42 percent of infants in

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the study had -- had measurement of the primary outcome of the hearing loss at 6 months of age, and, you know, this is really common in study -- you know, long-term follow-up is extremely challenging, particularly in the infant population. And so this was one potential issue with that study.
And then in the same study, the primary outcome was actually designated ahead of time, as is the usual process when creating a clinical trial. But that the study did not show the efficacy in the primary outcome, which was the hearing benefit at 6 months.
Even though hearing benefit was shown at 12 and 24 months, because it wasn't the primary outcome, specifically there was some, you know, reservation and thought that there needed to be even more evidence to be able to include information in the drug label. The next slide, please.
So, you know, there's also always the thought of developing new molecules or new routes of administration as we've heard about earlier today for this problem.

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But also, what about ensuring the appropriate use of molecules already on the market? And could PTN help to perform a well-controlled trial to add to the body of information to help establish efficacy. Next slide.
So the problem with considering another trial for symptomatic congenital CMV is that, you know, it's -- it's generally felt and assumed that there is going -- there is going to be a lack of equipoise.
And what do I mean by that? So the equipoise is the assumption that there's not one better intervention present, so we don't know whether treatment is better than no treatment. And even though there's, you know, according to -- you know, because of the issues I showed before, there's not extremely definitive data.
There's really compelling data to support treatment, and that's data that most clinicians are treating and most families want to be treated. So next slide.
So your -- you know, the -- the belief

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of clinicians and the belief of families when faced with this -- with -- with this disease is such that there -- there could never be a placebo controlled trial for infants with symptomatic CMV -- congenital CMV, moving forward, because no one would want to enroll in that trial, and, you know, it wouldn't -- it wouldn't be felt to be, you know, some -- there wouldn't be equipoise. So next slide.

And yet, we're stuck with the current drug labeling information where you -- you know, if you open up the package insert for ganciclovir or valganciclovir and you look under the indications, you see in ganciclovir, there's no pediatric indication -- and next slide, for valganciclovir there is a pediatric indication that it's for prevention of CMV in kidney transplant patients, so nothing that addresses congenital CMV at all, even though these drugs are used widespread. Next slide.

So where do we go from here? And we're -- we're -- we -- it feels, like, we're stuck. And so we -- I know this will be part of the discussion in the panels this afternoon. But, you

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know, there are some thoughts of -- of where we might go from here.

So could we use real-world data, so additional evidence from patients who are being treated with -- with congenital CMV now to provide compelling evidence to support changing these drug labels.

One issue with that is most patients are being treated with congenital CMV. So I think those with symptomatic congenital CMV are -- and are recognized, are being treated, and so it's really hard to know what the natural -- the natural history of untreated participants would be and to really find a great comparison group.

You know, PTN has thought about can we study something else unrelated and a related diagnosis that might have more equipoise to -- so that we could actually perform a trial in that population.

And next slide I'll -- I'll end with just some thoughts we have a little bit off of the current topic. But, you know, I think I heard some mention of postnatally acquired CMV earlier. And the

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discussion was that, yes, in term infants, it's really ubiquitous and -- and not an issue.

But in pre-term infants, postnatally acquired CMV causes a symptomatic stress just, like illness, and observational studies suggest that it's also associated with adverse long-term outcomes.

And you might imagine, you know, if -- if a full-term infant has CMV and it's -- it's contracted in utero -- a preterm infant who should be in utero still, but is now being taken care of in -- in the NICU and is born prematurely who contracts CMV might also have some of those same adverse consequences that infants who -- full-term infants who contract congenital CMV might have.

Many clinicians are actually using antivirals to treat postnatally acquired CMV. They're not approved -- also not approved by FDA for this indication, and not everyone is -- is treating, because I think there's still -- it's still unclear whether this is a disease that benefits from antiviral treatment.

So therefore, further studies are

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needed to determine natural history of postnatal CMV to develop potential trial end points. So a related topic, but just some thoughts of where we might go to study these medications more and that could potentially be applied to the congenital CMV space as well.

All right. And the next slide is my last. I thank you all for listening to me, and I hope you haven't gotten too hungry in the meantime. Thanks.

DR. HODOWANEC: Thank you, much. Thank you, very much, Dr. Greenberg. Wonderful presentation.

But we have just a few minutes now. We were supposed to really be starting lunch at this time. Sorry we got a little behind over the course of the morning.

So we're going to really limit it to just one or two clarifying questions. If it's a meatier comment or question, we'd like to save it for the panel discussion this afternoon.

Okay. I see that Dr. Bo has his hand

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raised. Before I go to you, Dr. Bo, there is one comment in the Q&A box that I would like to read first.

So we have -- from Alyssa Blake [ph] another -- not a question, but a comment. "Just wanted to, again, thank Dr. Pesch for sharing her perspective and info about congenital CMV.

I really appreciated her talk and approach to congenital CMV, which focuses on emphasizing supports for children with congenital CMV, rather than cures for neurodiversity and deafness and looking at CCMV as a spectrum, rather than all or nothing, symptomatic versus asymptomatic.

Her talk was very informative and gave a great nuanced perspective." Yes, Alyssa [ph], we agree wholeheartedly.

Now, I will turn it to Dr. Bo. Do you have a clarifying question or comment?

DR. BO: Yes, a quick clarifying question for Dr. Greenberg, and it should be really -- relatively quick, and if we don't have time, I think I'd love to have additional time during a

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discussion -- the panel discussion.

The question is, in the context of congenital CMV, therapeutic area, how well accepted is CMV viremia infection a surrogate marker of disease and poor outcomes?

I think we've seen that CMV viremia infection was a surrogate and effectively used in the context of a CMV infection posttransplant, either solid or stem cell transplant, but in the context of -- context of -- of CMV, I think this is something worth looking into.

DR. GREENBERG: That's -- that's a great question and I think probably -- you're right, deserves further discussion in the panel later on in terms of what we're thinking about, whether the trial employs what could -- that could, you know, make something -- these studies a bit more feasible.

You know, and I invite anyone else, you know, Dr. Kimberlin or whoever, to weigh in as well. But, you know, from an infectious disease expert -- as a neonatologist, this is something that I would definitely be asking my infectious disease colleagues

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clinically to weigh -- to weigh in on in terms of how often viral levels are -- are followed.

Certainly, in -- when we had infants with acquired CMV in the NICU, you know, we -- we will sometimes follow viral levels. But I think the evidence and relationship to outcomes is not entirely clear and probably needs to be further elucidated.

But that's a -- that's a great comment. I'm also seeing -- if it's okay, there's a question in the chat that I can address. There's a question about comparing -- a clinical trial comparing another medication, like the letermovir to ganciclovir, and could the PTN support a trial like that.

And I think, you know, that's -- that's a great question and a potential possibility, I think.

Certainly, we need to -- we would need to, you know, figure out from a programmatic standpoint of -- you know, particularly, since our focus is mainly on -- on off-patent medications, but if the comparator is something, you know, in an established off-patent medication, that is I think a place where we could explore involvement if there are

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other medications under development for the -- for congenital CMV.

DR. HODOWANEC: Thank you, Dr. Greenberg, and thank you, Dr. Bo, for that question. I think -- I think there's lots more to be said about that.

You know, as you pointed out, we really have had a lot of success in the transplant space where we have a lot more comfort with -- with viral -- virologic end points. But I think it's a little different in the congenital CMV space, and I know Dr. Kimberlin will elaborate upon that this afternoon in -- in our panel discussion. So look forward for more to come on that.

Now, one last comment. I see Dr. Schleiss has his hand raised. This will be the last comment before we go to lunch. Dr. Schleiss?

DR. SCHLEISS: Yeah, thank you. Clarifying question for Dr. Greenberg, whose talk was terrific, by the way.

I -- I wanted to ask your preemie data or your -- yes, your premature infant valganciclovir

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prescription data. I just wanted to clarify. Those are definitely congenital CMV babies that -- that were in your data set?

DR. GREENBERG: Great -- great question. So those were -- it's not -- that particular graph was not just limited to preterm infants. That was all infants with a congenital CMV diagnosis or diagnosis that occurred in the first 21 days postnatally.

So because it's retrospective data, we couldn't determine unquestionably that this is truly congenital CMV. Not all infants were tested at birth. And so -- but if they were -- it occurred during the first 21 days of -- of age.

DR. SCHLEISS: Okay. So I -- maybe I misread the slide. But I thought -- I thought the slide -- I thought you had one slide that was just for premature infants.

DR. GREENBERG: I did. But the graph -- the graph was for both term and preterm infants.

DR. SCHLEISS: Oh, okay. Well, we can

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talk more about this later. I -- I mean, I think one --

DR. GREENBERG: Yeah.

DR. SCHLEISS: -- discussion is what I perceive frankly to be the overuse of nucleoside antivirals in postnatal CMV infections in the newborn intensive care unit.

So I just wanted to clarify what -- if your data set for the premature babies sorted that out. But we can talk more about it later.

DR. GREENBERG: And that's something that's actually -- I don't think that we've -- we've looked at the incidents of treatment for postnatal CMV -- or we -- I know we haven't published those data.

DR. SCHLEISS: Yeah.

DR. GREENBERG: So it is something that we can look at, of course, the definition of postnatally acquired CMV also has to be, you know -- we -- we might say it's diagnosed after the first -- after the first 21 days of life. But if an infant didn't have testing early in life, it's possible

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that -- that infant may have had -- may have actually had congenital CMV.

So it's -- it's a bit hard to tease out with existing data. But we've -- we've attempted to do that in the past --

DR. HODOWANEC: Wonderful. Thank you all for the great questions. And -- and thank you, again, to our Session 2 panelists.

With this, we will go to lunch, and we will meet back at one o'clock for our -- for our panel discussion. Thank you, everyone.

(Off the record.)

DR. HODOWANEC: All right. Welcome back from lunch, everyone. The remainder of our meeting today is dedicated to our congenital CMV panel discussion.

As has been highlighted over the past day and a half, the conduct of clinical trials for rare conditions, particularly those involving the vulnerable neonatal population is generally fought with challenges. Trials for congenital CMV infection have their own unique set of challenges.

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Before congenital CMV investigational product can be studied in patients, there are questions regarding CNS and inner ear penetration that must be addressed.

Regarding clinical trial design, there are numerous questions regarding patient population, identification of meaningful and feasible efficacy end points and selection of a comparator arm that will provide interpretable data.

Over the next several hours, we look forward to robust discussion on these topics and others.

While we acknowledge the important potential role of both pre- and postnatal treatment of congenital CMV infection, for the purposes of this workshop, we ask that the primary focus of the discussion be geared towards the development of drugs for the postnatal treatment of congenital CMV infection. Next slide, please.

I would now like to introduce the following panelists for the first time. We have Dr. Tien Bo, Global Medical Head of the Transplant and New

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Programs at Takeda Pharmaceuticals, and Dr. Paul Griffiths, Emeritus Professor of Virology at the University College of London.

We also have numerous panelists and speakers rejoining us this afternoon, some of whom presented earlier today and others who presented yesterday.

Very briefly, our FDA panelists include John Concato, Dr. Lindsay DeVries, Dr. Ryan Kau, Dr. An Massaro, Dr. Lily Mulugeta, and Dr. Kunyi Wu.

Our external panelists, who have been previously introduced, include Dr. Roberta DeBiasi, Dr. Rachel Greenberg, Dr. David Kimberlin, Dr. Tatiana Lanzieri, Dr. Emma Mohr, Dr. Megan Pesch, Ms. Betsy Pilon, and Dr. Mark Schleiss. We are so excited to have so much expertise and so many unique perspectives represented on this panel. Next slide.

So the first topic that we would like the panel to discuss this afternoon is the key challenges in antiviral drug development for the treatment of congenital CMV infection.

So I will -- I know this is a very

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broad topic. But I just want to start there and see what initial comments some of our panelists might have about what they see as the most significant challenges.

DR. BO: Aimee?

DR. HODOWANEC: Yes. Hi, Dr. Bo. Please.

DR. BO: Hi. Thank you, very much, for that. I think one of the first things that I'd like for us to discuss through that's specific to this first -- number 1 area of focus is actually on the challenge of preclinical models and how could it inform us, even before we start doing clinical trial work in humans.

And I have a couple of just series of questions. I think I'd just like to ask that, and I think -- let's see how it -- it can be incorporated into the discussion.

Number 1 is with regards to animal model, Dr. Mohr presented, what's the feasibility of extrapolating the animal model of blood/brain barrier penetration from -- from the macaques or animal models

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to humans?

What's the relationship between the viral load and the severity of CMV -- of CMV clinical manifestations, including the symptomatology?

And what's the -- the relationship between -- axis -- even longer term treatment on adaptive immunity against CMV that may require a competent immune response to either inoculation challenge or -- or exposure to the virus?

I think -- to me, I think these are some of the questions that I like to think about when we're thinking about how to extrapolate in the context of the clinical trials and developing new clinical trials.

DR. HODOWANEC: Thank you for all of those wonderful questions, Dr. Bo. We -- we can take those one at a time, and we might need you to repeat the -- the second two as we go here.

But I think, you know, starting with your first question about using animal models or -- excuse me, non-clinical studies to help determine whether or not a drug penetrates the -- the human CNS,

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I think, is -- is a great question.

I don't know if Dr. Mohr has any initial thoughts on that, that she -- she would like to comment on.

DR. MOHR: Yeah. That -- that's a great question. And I'm not aware of studies that compare the fetal macaque blood/brain barrier directly to human fetal blood/brain barrier studies.

But I do know that, you know, comparing the fetal neurodevelopment sort of step by step, a lot of that is very similar. And there are some reviews that discuss this about when different -- when different stages happen.

And a lot of it happens in utero, rather than after birth, like they are in some other, like, hearing models. So that's very prompting as far as long-term exposure during pregnancy.

DR. HODOWANEC: Thank you, Dr. Mohr.

Yeah, I think, you know, this is something that we have thought about a fair amount, and -- and one of the other things that comes up sometimes along this line of thinking is that even

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within humans that, you know -- what penetrates the human blood/brain barrier at one age might not be the same as -- as at another age.

And -- and so I think -- I think that this is a really important topic for us to try to -- to understand better.

Yes. And, Dr. Viswanathan, then you have something to add?

DR. VISWANATHAN: Yes. This is Prabha Viswanathan. And I just had a follow-up question that's related to this, and this is really to clarify my understanding, Dr. Mohr.

You mentioned that there -- there seems to be a paucity of studies in -- in the postnatal period and certainly have been in the antenatal period and looking at the fetus.

I believe Dr. Bo's question was more about the -- the newborn neonate. But it seems, like, there's, again, a paucity of study -- of studies in this population more broadly and -- and curious whether there are any -- any factors that you have seen as -- as being prohibitive, other than the

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typical compliment of -- of cost and -- and those kinds of things.

DR. MOHR: Yeah. So I'll answer the first question first. So what are -- what do I think the factors are that have prohibited studying in infancy congenital CMV infection outcomes and interventions?

I think the biggest one is the model where you don't get 100 percent penetrant. So when macaque pregnancy studies themselves are, you know, $25,000 per animal, if you only get 5 out of 12, that actually have congenital CMV infection, how are you going to have large enough sample sizes to test an intervention and see if it works.

I think that is really challenging, especially when we know that there's a spectrum of congenital CMV disease in -- in infants. I think that's a really large factor here.

Sorry. I forgot your first question.

DR. VISWANATHAN: It was just a kind of clarifying question about whether we -- we could -- if we did have some data about a fetal blood/brain

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barrier, whether a rhesus macaque correlates with a baby, could we then correlate that with the newborn?

DR. MOHR: I don't -- I don't know if that answer is out there or -- or available. I think that is a really good question, and I don't know if those studies have been done to look at both fetal blood/brain barrier permeability in the macaque and also in -- in the neonatal macaque.

Those are good questions. Mark Schleiss has his hand raised, and he's also in this field, and he might -- he might know a little bit about this.

DR. SCHLEISS: Yeah. I -- I don't -- I don't know the answer to that question, specifically. I mean, my experience is more with rodent models, getting pink models.

And we -- you know, the newborn mouse, for example, is very much immunologically -- or embryologically like a fetus, and so studying newborn mice might be more relevant to humans in that aspect.

But I want to step back for a second and just sort of think about the issue of antivirals

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and the blood/brain barrier. We heard this morning the comment, which I agree -- agree with, that the damage was already done by the time the baby is born.

And so, you know, the CISG 112 study did show some preservation of neurodevelopment. But -- but do we really think that antivirals in the infected neonate are having an effect on the infant brain with respect to CMV sequelae, or -- or should our goal really be to try to mitigate ongoing bowel replication in the cochlea?

And -- and so what do -- what do we hope to gain with antivirals to begin with in terms of neurodevelopmental outcome and congenitally infected babies?

You know, just thinking about the biology of the virus and the timing of fetal brain infection and the fact that it's almost unheard of to find CMV in the subarachnoid space in a newborn, by that time, has the brain infection already sort of burned itself out and -- and are we really going to gain a lot with antivirals?

I don't know. Just trying to be a

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little provocative here. But curious what the other panelists think about that.

DR. PICA: Thank you, very much, Dr. Schleiss. In one moment, I'll call on Dr. DeBiasi there.

I guess sort of one just quick follow-up question that I had to your comments there, you know, we talk about the blood/brain barrier. But I think to your point, one of the things we're particularly interested in is whether or not the -- the drug is getting to the inner ear.

And so do we need to -- you know, how do we determine that? And so do we need a drug that can penetrate the blood/brain barrier to say that it's reaching the inner ear. Do we know the answer to that question?

So I will leave that question, and if others have any follow-up comments on that, I -- I would -- would be very interested to hear it. Dr. DeBiasi?

DR. DEBIASI: Sorry. I just wanted to go back and see perhaps if -- I don't know if Dr.

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Abzug or Dr. Kimberlin is -- is still on. But could we just summarize what we know about the viral -- you know, the -- the kinetics of the virus in those CSG settings that were done?

Because, you know, my takeaway from that was, yeah, we suppress the virus, but it comes right back up. But, yet, we still saw this effect.

So to me, that means that, you know, it may -- there may be some -- antiviral effect is probably important for some aspect of the hearing outcome, but probably not the whole thing or, you know, it wouldn't have been as effective as it was.

And then, you know, to Mark Schleiss' point, you know -- and I think I said this earlier, we do have to think carefully about what the outcome we're looking at, because the most severe outcome, for instance, following microgyria in a completely structurally abnormal brain, is not going to be affected by antiviral treatment.

So, you know, we -- we wouldn't want to assess the efficacy of an antiviral treatment by lumping all the outcomes together; right? We would

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want to be careful about thinking, well, what are the -- what are the deleterious outcomes that could be affected by an antiviral, or if you don't know, be able to at least post-talk look at different aspects of the outcomes. Otherwise, if you just lump everything, you -- you probably lose the effect.

But I see David is raising his hand. So maybe he could tell us a little bit about the virology part of it.

DR. HODOWANEC: Thank you, Dr. DeBiasi. Dr. Kimberlin, we'd love to hear from you on this. And then also, Dr. Griffiths would like to comment on some of these viral load related questions as well.

Go ahead, Dr. Kimberlin.

DR. KIMBERLIN: Perfect. Thank you for -- for a fantastic morning. And -- and I think the afternoon is going to be really interesting as well as these conversations unfold.

In my -- my thinking on kind of the arc of the -- of the studies that the CASG and -- and now the Congenital and Perinatal Infections Consortium have undertaken with congenital CMV is that it --

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it -- the only way I think you could say that you have the improved hearing outcomes that we see, is either it was just by chance alone or there's an antiviral effect specifically on the inner ear.

That -- that blood inner ear barrier is -- is where I think the -- the likely activity is happening -- drug getting into the inner ear and having an effect on virus.

And we know from explants, when people have cochlear implants, at least in a handful that have been looked at, there are some that still have CMV DNA, even in a 5-year-old, a 4-year-old, when the -- when the cochlea is removed, so in -- in the explanted material.

So I think that the idea of whether it's only that, there could be inflammation as well. There could be a host immune response. I don't know. But -- but I do think it would suggest that there is -- there is active viral replication.

And at least with respect to ganciclovir and valganciclovir, there is some suppression of that and, hence, the more favorable

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outcomes that we saw within the studies.
I do think we have to think about the study designs. It was pointed out, I think, in one of the slides -- correctly pointed out that we had a lot of loss to follow up in the old ganciclovir treat/no treat randomized trial.
That's a cloud that hangs over that study and always will. You can't go back and -- and un-ring the bell. But if it -- if -- if what we saw in that study was by chance, which I don't think it was, but if it -- if it were, then the -- how do you explain the 112 study, six weeks versus six months, where the longer treatment had better outcomes at a year and two years?
So I -- I think the totality of the information is -- building on a series of comments I made yesterday, looking at the whole story being told across these studies, suggests that there's benefit -- audiologic benefit -- maybe developmental benefit.
That was really more of -- that was just the 112 study alone. So I -- I'm -- I think that's a little bit softer ground personally.

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In terms of viral load -- blood viral load, this has been brought up a couple of times, and -- and Dr. Griffiths will be able to -- to put it in a broader context with respect to transplant and so forth.
I will mention that Concetta Marsico was -- or is an Italian who came and worked with us for seven or eight months, something like that, in the late 2010s and did a really deep dive into the CASG PCR data. And she did find -- and it was, I think, a 2019 JID paper, she found a statistically significant difference where the people that were having worse hearing outcomes had higher blood viral loads.
But there was an awful lot of overlap. There were some that had terrible hearing outcomes with very low blood viral loads. There were some with very high blood viral loads who had normal hearing.
And so it -- you know, statistically, yes, it means something. Clinically, I think it's a harder thing to -- I -- I don't think it can be a biomarker in the way that, you know, perhaps Dr. -- Dr. Bo would like for it to be a biomarker for

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example.
But I want to hear what Paul says, because he knows a lot more about this than I do.
DR. PICA: Thank you, Dr. Griffiths -- or sorry, thank you, Dr. Kimberlin. Dr. Griffiths, would you like to add some comments?
DR. GRIFFITHS: Yes. Thank you. Let me go back to the question that was asked just before the break, if there's a possibility of using measurements of viral load and the way that they're done in the transplant patients.
If we just go back in history, the stem cell transplant patients were being monitored increasingly with methods that were becoming more rapid, particularly, PCR.
And so clinicians could note, almost in real time, that patients who had viremia pretty rapidly went on to get CMV end organ disease, whereas the patients who didn't get viremia had a very low risk of getting no end organ disease.
And this led to the interruption of preemptive therapy where ganciclovir and

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valganciclovir were given in people with viremia to stop them getting end organ disease.
And of course, regulators, like the FDA or EMA, will want better data than that to actually convince them that this is a reliable marker. And extensive trolls of the literature were done to show the viral load did, indeed, correct the disease, that there were low risks of false positive and false negative associations, et cetera. I can find that paper and send it back to the -- to the panel afterwards.
And this led to ultimately so called "clinically significant CMV infection," being a agreed as -- as a usable primary end point for phase 3 clinical trials.
But it's important to recognize that -- that is the clinical decision of the clinicians looking after those stem cell transplant patients to prescribe valganciclovir, which is toxic to the bone marrow that they have just engrafted.
So they only do that if they're really convinced -- virtual connectivity interruption --

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unilateral hearing loss, a risk factor for getting bilateral hearing loss, because we have to think that their other ear may be being challenged by virus coming in that bloodstream.

It's obviously not -- not coming directly from one ear into the other ear. It may be going via the bloodstream, and that would be a very doable thing to do in the natural history of study -- doable question to ask.

Thank you.

DR. PICA: Thank you, Dr. Griffiths. We really appreciate your -- your perspective and providing that additional transplant context.

I think Dr. Schleiss had his hand raised next. Dr. Schleiss?

DR. SCHLEISS: Yeah. Yeah, thanks. Paul, thanks for that comment. I -- I just wanted to mention a little bit of data that we have that's unpublished. I'm still trying to sort it out.

But, you know, we were very interested in this universal screening study at the viral load at the time of birth in saliva and dried-blood spot and

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the likelihood of symptomatic disease upon follow-up of these infants.

Most of the viral load studies in congenitally infected babies have a really strong selection bias, meaning these are the sickest kids, because they are the ones that are identified as having something wrong.

And so they get an assessment. They have viral load studies done. They're referred to tertiary care centers and clinics. But what -- what do we know from an unselected population?

And the P value isn't quite significant. But -- but there really does seem to be a trend toward higher viral loads in the asymptomatic babies. And I think I know the reason why. You know, the fetus has an immune system.

And I think that some of the sickest babies I've seen are the ones that have early gestation infections where the fetal T-cell response has weeks, even months sometimes to kick in and control viral replication, at least to some degree.

Some of the highest viral loads I see

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are in women who have very convincing histories of third trimester primary infections. And those newborns simply haven't had the time to make an immune response to help control their -- their infection. They have high viral loads. But they're asymptomatic.

So I -- I think this is going to end up being complex, and I don't think it's going to be sort of the simple calculus that we see in infectious disease practice where high viral loads usually mean something bad. I don't know that that's going to be the case.

Now, you brought up an interesting point about systemic viral load and what's going on in the cochlea, and I think that is a little bit of a different situation, because that's an ongoing infection that may percolate for weeks, months, maybe even years.

One thing I do worry about is compartmentalization in children who have good peripheral viral load control. I don't know that their cochlear CMV strain, if you will, is going to retain susceptibility to ganciclovir.

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We do know that in both transplant patients and in some congenitally infected infants, we do see compartmentalization of strains that have varying degrees of ganciclovir susceptibility.

So anyway, just a couple of comments, but I thought I'd share that with the group.

DR. PICA: Thank you, Dr. Schleiss.

DR. VISWANATHAN: This is Prabha Viswanathan again. Just one follow-up -- follow-up question, and then we'll turn to you Dr. DeBiasi.

I'm curious whether there are any data available about whether the cochlea -- the inner ear is -- is a sanctuary site for virus, whether we know if there is an immune response there, whether cells are able to get there -- the immunoglobulin is able to get there and -- and then would -- would a drug be able to get there. We know virus does.

I see Dr. Kimberlin, you have your hand raised. Please, go ahead.

DR. KIMBERLIN: I -- I don't know the answer for sure. There are pretty rare instances where a person who had congenital CMV would, usually

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when they're in their teenage years, have a very abrupt loss of hearing. Like, they go to bed at night with stable mild hearing loss, and they wake up deaf.

To me, that -- that would be harder to -- to think of as -- for that example, as a virus-induced hearing loss. It's too abrupt. It sounds immunologic to me. If it is immunologic, then it has to be some sort of immune response in the inner ear where the hair cells are.

And -- and I would think -- and the way I'm thinking about it anyways, so the implication to me is that, yes, there is an -- there is immunology going on in the inner ear. But I -- I don't know that it's been certainly studied as well as it should, if studied at all.

DR. PICA: Thank you, Dr. Kimberlin. Dr. DeBiasi?

DR. DEBIASI: Yeah. I just had a couple other follow-up questions from some of the comments that were just made by Dr. Griffiths.

So do we have any information about viral loads longitudinally in -- like, you know, we're

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following them. They have normal hearing -- normal hearing. We're following them clinically over time. I know in the CSG studies, we haven't been able to then, you know, follow viral loads over time and try to correlate that with their hearing loss. So that's just one question.

The second point was, you know, we're talking a lot about, you know, should viral load be a big part of decisions about designing the next trial.

To me, it seems, like, you know, if we -- if we believe the studies that have been done -- and I do, that there must be some antiviral effect.

It seems, like, you know, whether or not we can prove it beyond what has already been done, in practice, people are going to be using antiviral, so maybe we should be focusing more on antiviral, plus or minus other things, to improve the outcome.

So those were the two points. And then the last thing I was going to ask about if people had thoughts, you know, just like in COVID, we've seen that children who get reinfected may have different outcomes than kids that don't get reinfected.

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Are there changes with long-term effects with, you know, continued reinfections? Could that be the case also with CMV?

So that a congenitally infected child, for whatever reason, if they're one of the few that are very symptomatic and have outcome -- bad outcome either with neurologically or with their hearing, are they actually more susceptible to -- you know, they're going to get exposed to CMV out in the community over time as well, is there something that them, in particular, need to know that would explain repeated infections, you know, making disease even worse?

Those are just thoughts that came up.

DR. PICA: Thank you, Dr. DeBiasi.

It looks, like, Dr. Griffiths has his hand raised to respond.

DR. GRIFFITHS: Thank you. So to try to address those, the first question, should we be measuring serial viral loads? Yes, I'm sure we should to help understand natural history, first of all, secondly, to get a pharmacodynamic response to the administration of the drug, does the viral load come

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down in, say, the urine or -- or the saliva, and then thirdly, to look for correlations, which may help to understand the pathogenesis of disease.

If you control the virus load in the urine or saliva, does that correlate with the ability to control hearing loss? And those were put into the -- the last study that David organized in the children age 1 month to 4 years of age. We were going to look for correlates of efficacy -- of outcome.

Unfortunately, the study didn't show a clinical benefit in hearing loss, so there's no analysis to be done in those terms. But at least there was a reduction in viral load in those biometrical samples.

And then, you know, second point to that, should we be thinking of adding in something else, like an anti-inflammatory, partly for the reasons that Mark Schleiss has mentioned.

I think that's really quite interesting, and it would -- certainly is wrong to think of the virus as the bad guy and the immune system is the good guy. They can flip over under

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certain circumstances.
But can you define what those circumstances are so that you minimize the risk of administering other particular drugs?
DR. PICA: Thank you, Dr. Griffiths. Excellent points.
Dr. Schleiss?
DR. SCHLEISS: Yes. And I -- I just want to weigh -- you know, cast my vote. Definitely, we need to have viral load monitoring as a part of an antiviral study. No question about that. I mean, we need some kind of biomarker to look at whether the antiviral is having an effect.
I'm just unsure if the viral load, especially early on in infancy, is a predictor of outcome. But it's a parameter you have to measure.
One thing I've always wondered about too is, as in the transplant setting, maybe a little bit of a DNA-emia is a good thing, because it trains your T-cells to help control the infection long-term.
But there's a very interesting and I think important paper from Soriano-Ramos, the citric

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study in Spain that's just -- just came up on PubMed three, four days ago, in which they looked at interferon gamma CD8 and CD4 responses in infants with congenital CMV and didn't find any correlation between CMV specific CD4 and CD8 T-lymphocyte responses and long-term sequelae.
So although I think that's another parameter we need to look at, it doesn't appear that the education of T-cells in the congenitally affected infant is a predictor of sequelae of either.
DR. PICA: Thank you, Dr. Schleiss.
Dr. Kimberlin?
DR. KIMBERLIN: I'll just mention that we do have a study that was started when we still called ourselves the CASG, a CMV biomarker study, that -- where we're -- we're hoping -- we're going to be looking at a -- or we are looking at a number of different things, transcriptomic, cell mediated, humeral viral load.
And -- and the idea there hopefully would be with -- if -- if no one of those is a single biomarker, could there be a composite biomarker that

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might be able to be developed?
Because it really would be extremely helpful, obviously, if we could -- if we could make such an identification.
That study should enroll through next year. So hopefully in 2026, we'll begin to have some -- some data from that.
DR. PICA: Thank you, Dr. Kimberlin. And can you just clarify, how long is the follow-up? How long are you collecting these samples determinedly?
DR. KIMBERLIN: The follow-up is only two years. And that's a whole other issue with -- with respect to the way these -- these studies are funded.
You know, what we all want is exactly the point made earlier, we want to know what happens after adolescent, you know, years if possible. But the funding cycles don't allow for that.
They'll stretch out five years by the time you write the protocol, get the study enrolling, have time to clean the database, analyze, do your

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final study reports.
It's -- it's an artificial framework that we put on what is a natural process from the virus and the host.
We do have -- and -- and I -- I dashed away during lunch and saw one of our study subjects. We have a follow-up study, one of the CPIC studies, bringing people back who had been treated as an infant for congenital CMV.
And of course, they're going to be anywhere from, you know, 4 years of age or, you know, 6 years of age, something like that, out to the 15-year-old and older that I saw today to see whether -- mostly what the durability of hearing is.
That's going to be sort of, I think, discernable. It's not -- it's a -- it's a one-time visit. So it's going to -- there will be some weaknesses to it.
Also, what their development is and what's happened with respect to any toxicities. You know, have they entered puberty as would be expected, for example? Have they had any kind of cancers?

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Because as we know, ganciclovir in animal -- some animal models can be carcinogenic.

So -- so we'll have some additional data there. But it's not the same as following the same cohort sequentially over many years. That's simply not feasible, at least with the funding mechanisms we've been able to identify so far.

DR. PICA: Thank you, Dr. Kimberlin.

Dr. DeBiasi?

DR. DEBIASI: Yeah, I -- I'm excited to hear about that, and that was actually going to be my next question is, do we have planned or have we done any kind of cytokine, proteomics, transcriptomics analyses, but not just of the severely affected kids, but a comparator to the asymptomatically affected kids?

Because as always, there's a big amount of noise when you're trying to find those biomarkers, and having that control group is important, if you can. So just curious about that too.

DR. KIMBERLIN: Yeah, that's an excellent question. And Octovio Ramios' [ph] group

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has done some of that work with both what we -- I don't know if we're going to keep calling them "asymptomatic" and "symptomatic" -- I'm not sure what the terminology will be, but using that older terminology, they've done -- Asumit Haes [ph] has done beautiful work.

Nature's -- one of the nature journals published it, with identifying a transcriptomic signal -- seven genes if I remember correctly.

And, well, that's -- we're partnering with her on the biomarker study to -- to be able to hopefully have some application of that to a test population, not just a development population.

I -- I want to clarify something. I think I said out to two years for biomarker. It's going to be out to -- for some of the subjects -- those enrolled farther back, out to 3 years of age. But still, not out to 8 years, 9 years, 10 years of age, like we really would like.

DR. PICA: Thank you, very much.

DR. VISWANATHAN: There's one comment in the Q&A that we'd like to share, and I'll just read

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this. It's from Laura Gibson.

"In general, antimicrobials work best as a support for the immune system, which in children has variable capacity, depending on gestational or post -- postnatal age.

Could we use therapeutic vaccines or other immune based therapies for infants or even fetuses with or without antivirals? I think this would be an important approach to study."

We wanted to share this concept as we were talking about adjunctive strategies to antivirals. I do think that these immune based therapies and therapeutic vaccines are a little bit out of scope of this conversation, but did want to share this idea with the group, because I think it's a great point.

DR. PICA: Thank you.

Dr. Bo, so I think we've covered your first question and your second question. But can you remind us your third question? Have we tackled that one yet?

DR. BO: Yes. No. Thank you, very

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much. And actually, on the lines of -- I think one of the questions -- I think any -- involving small babies is the small volume of tissue and blood that you can expect --

DR. HODOWANEC: Dr. Bo, I'm sorry. We're having a hard time hearing you.

Are others having difficulties as well, or is it our connection? Others are as well. Okay.

DR. BO: Let me -- let me -- yeah, can you hear me now? Better?

DR. HODOWANEC: Yes, that's better.

DR. BO: Perfect. Thank you. In essence, one of the challenges associated with conducting clinical trials is collecting blood or tissue samples from small babies.

And so the question that I have for the panel to -- I'd love to -- to, of course, to discuss through this, what are the clinical feasibility and medical justification considerations on the prioritization of required blood draws or tissue samples or cerebral spinal fluid collections and burden on babies in this patient population?

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DR. HODOWANEC: Excellent question, Dr. Bo. I think everybody is thinking about it in their minds.

Please, feel free to raise your hand if you have something to add.

DR. KIMBERLIN: I don't have -- well, I know what the -- the parameters are. It's 3 -- 3 mLs per kilogram over 24 hours or 7 mLs per kilogram over six weeks, depending on local IRB versus NIH guidelines and so forth.

I will say -- and FDA, please, you know, weigh in with what -- if you all have parameters I'm not aware of.

If you -- if you look back at CASG studies -- and this could be neonatal herpes or -- or the neonatal enteroviral sepsis or the congenital CMV studies, we have in the method section what the minimum weight is, and there's nothing magical about it, except it's a measure of blood out.

How much can we -- what -- what's the lowest weight that we can enroll and -- on that 3 per kilo or 7 per kilo, whichever we're looking at, not

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take out more for research related labs in that threshold?

So it has a direct impact on the way -- on the decision on who gets to enroll in the studies.

DR. PICA: Thank you, Dr. Kimberlin.

Dr. Schleiss, did you have something you would like to add?

DR. KIMBERLIN: Well, at the risk of shifting topics for a second. But I did want to just sort of go back to this issue of the carcinogenicity of ganciclovir, which I -- I don't think is really a big issue, but maybe -- maybe Dr. Greenberg has a comment on this.

You know, we've been seeing some of our pharmacies in the Twin Cities starting to raise this issue, and to the point of this should be treated like you would treat chemotherapy; the parents need to wear gloves before they try to administer the medication.

It's sort of dþjþ vu all over again, because I remember this stuff being discussed 15 years ago, and then I -- I really haven't heard much about it for a long time. But now the pendulum seems to be

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swinging back toward increased risk.

There was this paper, of course, that got a fair bit of attention in Genome Medicine -- I put it in the chatroom, on ganciclovir induced mutations following various transplantation settings, which I don't know if that has percolated out into the pharmacy circles or if -- of -- or if this is just anecdotal.

I mean, again, I just -- I haven't heard much about this in many -- many years. And it seems to be on the radar now of our local pharmacies.

So I wondered if others had this experience, if you had any comment on this from a regulatory perspective, Dr. Greenberg, and from a scientific perspective, is this really something we really need to worry about?

DR. GREENBERG: Yeah. Thank you for -- thank you for sharing. I hadn't -- I hadn't seen that article before.

But I think it underlies this potential long-term risk and the importance of studying any medications in infants and children, because the --

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the length of time after exposure that they have to experience adverse effects, even long-term adverse effects, is -- is substantial.

So, you know, you -- you bring up a very important point, and the reason why it is important to do -- to do these -- to do these studies.

Now, to -- you know, I think it -- it highlights the importance of sort of that post marketing follow-up and how, you know, we could put together, you know, their different ways to -- to do that.

But, you know, should every -- every patient who -- who is being prescribed this, you know, could we -- could we have a registry? Could we have something so that we could capture these data more symptomatic -- more systematically?

And I think it -- it also, I think, highlights the reason why, you know, we have these stops in -- in place of, you know, why there is such a burden of -- of proof for safety and efficacy to get something into the -- into a drug label.

I don't know whether this is the thing

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that -- you know, weighing risk and benefit, that that's the -- you know, that this is enough of a risk to -- to be a concern.

But it certainly leads one to stop and think, particularly in the postnatally acquired CMV, which again, is a totally -- you know, it's a different topic.

But there are some places that for certain patients with what appears to be symptomatic postnatally acquired CMV, that they're -- they're treating with these medications. And so I think -- I think it -- it's all important points. I don't think I have an answer. But interest -- interested in what others think as well.

DR. SCHLEISS: From a practical perspective, do -- do parents need to be wearing gloves and treating this as a chemotherapy?

And -- and I just want to echo your other point about the importance of registries. There is an association between congenital cytomegaly virus injection and acute lymphoblastic leukemia in childhood, an unproven association I might add.

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But -- but it just shows you how complex this is going to be unless it's really carefully dissected out in perspective studies.

DR. PICA: Thank you, all.

Dr. Pesch, I'm wondering, you know, this discussion about, you know, whether people who are receiving ganciclovir, if ganciclovir needs to be treated like chemotherapy. You know, you had talked a lot about other CMV parents talking about their experiences with being treated, like, you know, that they were very contagious and all of these precautions.

Have you heard anything to that effect regarding treatment or more infectious concerns? Is this something that -- that comes up within the -- the patient and parent community?

DR. PESCH: Yeah, it comes up quite a bit. I mean, families are -- are often overwhelmed with the worries of, I think, carcinogenicity and also, like, fertility concerns as well.

So we often have -- I see families popping up, saying our -- you know, "We -- we talked

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about these side effects. We're really worried." What -- you know, asking the group kind of what -- what would they do.

A few people have popped up with pictures of their prescription bottles with the chemotherapy kind of label on it -- I remember my daughter had that on hers as well, and, you know, asking kind of for group consensus, because I think there's a lot of confusion.

So, you know, if the label should be there, and if that is the safe thing to do, then that's one thing. But it certainly is adding to a lot of anxiety if -- if it isn't warranted, so hard to say.

DR. SCHLEISS: I've had parents refuse therapy, Megan, precisely for this reason.

DR. PESCH: Yeah.

DR. SCHLEISS: For babies that really should have been treated.

DR. PESCH: Right. Yes.

DR. HODOWANEC: Very interesting. Thank you, all. Anybody have any additional comments

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on -- on this topic, the -- the -- you know, the greatest challenges or additional preclinical, nonclinical work that could be done before we move into question number 2 for this first panel session?

DR. MOHR: I wanted to add something to the discussion on the -- the really long long-terms of antiviral exposure.

And I wonder -- you know, doing studies on this now sure will get answers in 20 years. But that doesn't answer the question immediately for people that want to know.

And I wonder if, you know, looking in electronic health records retrospectively could give signals to something like this.

And no -- obviously, no individual healthcare system is going to have the numbers required to do this, but something that, you know, combines multiple electronic healthcare systems.

I know the -- the electronic health system Epic has -- you know, combines all -- all systems together in a huge research database that you can access when you pose some special questions called

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the "Cosmos."

And you can get access to, you know, deidentified data through all of this, but they have a research team where they can ask these sort of questions.

It's really interesting the different work that they can do. But you could somehow figure out how to pose a question. Like, over the last ten years as babies have been prescribed valganciclovir, are there more signals for, you know, childhood onset oncologic diagnoses? And I would imagine that's something that their database may be able to do.

DR. BO: Yeah. As exciting as that may seem, I think one of the -- you know, the challenges Mark -- Mr. Schleiss mentioned, which is there are viruses that have the potential to be oncogenic.

On top of that, I think the patient population is so heterogeneous. Even in transplant, we see that it's not only the patient's primary disease that contribute to oncogenic potential, but it's also polypharmacy multi-medications.

Immunosuppressive agents is also

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relationship -- in connections with oncogenic potentials. Hence, I think the complexity of the so many different factors might require a greater intelligence.

DR. PICA: Thank you, all, very much. Oh, I see Dr. John Concato has -- thank you, very much.

And so for those of you who were not able to join us yesterday, Dr. Concato gave a wonderful presentation on the potential role of real-world evidence for -- for these two conditions that we're discussing at this workshop.

Dr. Concato?

DR. CONCATO: Yeah, I agree with the last two comments -- or the question and the response, that while it's theoretically possible to look in electronic health records, the complexity is not only considerable, it's -- it's daunting.

Not to throw up one's hands in advance before trying, but there is heterogeneity across healthcare systems. There is heterogeneity within the healthcare system, and that's before we get to the

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heterogeneity, unfortunately, of the CCMV itself and all the various attributes that we've heard about today.

So, you know, electronic health records are helpful. But we don't fault the clinicians for not recognizing that the data might be pulled later for research of protocol.

And in a different context, I often say, you know, we're not talking about randomized trials right now. But randomized trials are wonderful for two reasons. One is randomization. The second is the protocol that dictates the high-quality data that's collected, and that's hard to come by retrospectively. Although, it should be explored or can be explored.

DR. PICA: Thank you, Dr. Concato. Appreciate your perspectives. Well, we only have a little less than 15 minutes in this first panel session.

So I'd like to at least briefly turn our discussion towards the second topic, which is discuss the potential strategies that could be

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considered to improve collaboration between industry, academia, and parent caregivers to facilitate antiviral therapeutic development for the treatment of congenital CMV infection.

And I'll throw in there even that in addition to that, also collaboration -- potential legislative work, the base of some of our talks that we heard this morning as well.

What -- what additional collaborations could help move -- move the field forward?

DR. BO: You know, on this part, I just need to get something out there really quick, just to admire Dr. Pesch's passion behind her presentation of this and how moving it was for me to hear Dakota's story.

And Dakota's story of -- the issue of liability comes in so much that in some ways, it's -- it's a really challenging barrier for, I think, patients for industry, for regulators, and for the legal system to try to reconcile with.

It's such a big issue that I think if somehow there is an agreement on this front, it could

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really unleash a lot of the innovation in this space because of the -- the -- that this barrier is removed.

DR. PICA: Thank you, Dr. Bo.

Dr. Kimberlin?

DR. KIMBERLIN: So focusing on -- on question number 2, I spent about three years working with Roche gratis, no -- no compensation or anything, just -- just trying to help as they interfaced with FDA to try to get a breakthrough designation status or an orphan drug status for valganciclovir, as I recall.

And -- and the -- ultimately, that -- they pulled out of that process, because at least my recollection is that what was proposed back is that we would have to do another phase 3 study.

So to some extent, I think this is a very appropriate question to have. I would add in there, in addition, what could FDA do to -- to facilitate industry having a path forward in a timely enough fashion.

Especially thinking about valgan and ganciclovir, these are all patent. I mean, these -- they had -- they were just doing this out of -- truly

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out of the goodness of their heart. They didn't have anything left to -- to gain from it, at least not that I could see.

So I think that has to be part of the conversation as well. And I'm going to stop there for right now. I have another -- another comment that I -- I'd like to see if that gains any traction from conversation here.

DR. PICA: Thank you, Dr. Kimberlin.

I would just briefly say before we open it up to other panelists to respond to your comments, you know, we really are not able to engage in any product specific conversations here, which I understand is very challenging, given the large role that valganciclovir and ganciclovir play in the current landscape.

But in terms of the development program for any specific product, we at least, as -- as the agency, are not going to be able to -- to go down that path today. So I will stop there and see what other comments people might have.

DR. BO: Something really quick from an

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industry perspective regarding strategies that could help enhance or accelerate the transfer -- the investments in the space to produce -- transport the medicines for patients would be, I think, something that is already -- is in existence, and that is the accelerated review pathway and then the full approval pending confirmation of clinical benefit.

I think that's something that could -- could be reminded and potentially discussed in -- in ways of how primary -- the selection of primary outcomes for clinical trials could also be integrated into the accelerated approval pathway.

DR. PICA: Thank you, Dr. Bo. We -- we definitely will be talking about end points as a large part of -- of the second panel session. And I understand sort of all of these topics are so intertwined it's hard to really compartmentalize these discussions.

But we will certainly be talking about -- about potential end points, and we can have additional discussions about potential accelerated approval pathway.

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Again, I think we've heard a lot of hesitation regarding a virologic surrogate end point based on the data that is available. But -- but we can certainly have -- have further discussions about that.

Dr. DeBiasi?

DR. DEBIASI: I was just going to ask if, you know -- getting to the point here about how can parents and caregivers play a role here to improve collaboration, have there been any PCORI studies to just identify what are the -- the highest priority concerns of the target patient population in families?

I was involved in some of those for Kawasaki disease studies in the last five years, and it's actually very -- very interesting to -- to see that there's not always complete alignment between what we think people want us to study and what they actually would like us to study.

So I was just curious if that's been looked at in a PCORI-like way for congenital CMV.

DR. PICA: Thank you, Dr. DeBiasi.

Dr. Pesch, I see you have your hand

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raised.
DR. PESCH: Yeah. I think there were a couple of PCORI studies funded well over ten years ago. But nothing has made it to publication, and I -- I agree, it's high time and low hanging fruit in terms of opportunity for funding.
I think over the last ten years, the National CMV Foundation has been around for ten years now. CMV Canada is growing. There's CMV Action in the U.K.
And so these family organizations, I think, have really grown and are picking up momentum and very eager to collaborate.
I'm -- I'm always just so blown away by the -- the generosity of these families. I just wrapped up a study of 300 CMV families, and everybody did it for a sticker and a thank you card -- like a bumper sticker and a thank you card.
They're very eager, I think, to help in the next generation and, you know, those yet to be born. So I think that's one way to really increase collaboration is just to ask.

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DR. VISWANATHAN: Thank you, so much, for those comments.
And before we go back to Dr. DeBiasi, Dr. Kimberlin, I just want to note that FDA is -- is really very invested in getting the feedback of -- of patients and caregivers to -- to talk about what is truly clinically meaningful, because we academically have an idea of what is -- is the most powerful end point or the most impactful end point.
But it doesn't always align with really what families are looking for. As Dr. Hodowanec already mentioned and -- and Dr. Pesch mentioned, we had convened earlier a patient listening session, which gives FDA the opportunity to hear from a small number of patients really about their clinical -- their experience, their stories.
And we also have a mechanism called a "Patient-Focused Drug Development Program," which is more formal and allows for a larger venue and a larger audience for participation and can be attended by patient advocacy groups, individual patients, professional societies, many of the key stakeholders

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that will be really needed to propel this forward and something that we, as a community, can discuss as an avenue for next steps as well.
But I do know we are -- our clock is ticking down, so let us turn it back over. Dr. DeBiasi, please, go ahead.
DR. DEBIASI: Oh, I just -- I was going to follow up to Dr. Pesche -- Pesch. I'm sorry. I'm saying your name wrong.
Do you have a sense -- just I know there are all these mechanisms to formally assess, you know, what patients want. But, you know, since you're in that, interfacing with those groups and part of that, do you have a sense of, like, what is the hot -- like, what is -- what do people most want?
DR. PESCH: Well, it's not hearing loss that they're most concerned about.
DR. DEBIASI: Right.
DR. PESCH: And not to discount the hearing loss or the impact --
DR. DEBIASI: Right.
DR. PESCH: -- but honestly, so often

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I'll talk to families, and we're all, like, "Oh, well, it's just hearing loss." Like, the MRI is clean. So far, it's just hearing loss.
So I think it's those kids that have the -- I mean, I think probably the biggest topic are those kids that are -- have kind of the mild CNS involvement, the white matter, the lenticulostriate vasculopathy that no one really knows quite what to do with.
And then later on, it's the gross motor stuff, the kids who can't -- who struggle with ADLs and independence. And then intertwined with that, we just see so much with autism. And I do --
DR. DEBIASI: Yeah, and I -- that -- that's exactly what I was expecting to hear, just from talking to my own patients that -- not that all the work that we've already done is not important. But it might be time to reassess, like, what it is that we actually want to focus our energy on.
Because I think those things you just said are the things that are -- people are most concerned about and that we have the least information

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about.
And we don't, you know -- we have cochlear implants. We don't have ways to fix unknown white matter, you know -- so I think that's a really important point.
DR. PICA: Yes. Thank you, Dr. Pesch. I -- I think, you know, that -- that makes a lot of -- a lot of sense. And I think it really helps us sort of frame some of our ongoing discussions about end points in this next session here. But it's such a really helpful perspective for us to have. Thank you.
So we are almost at breaktime. We will hear briefly from Dr. Kimberlin and Dr. Bo, and then we will be going to break.
DR. KIMBERLIN: And -- and mine is a deflection to Dr. Greenberg. I'm -- I'm interested in -- in the PTN and C-Path efforts from a couple of years ago. And then I stopped hearing about it with respect to valganciclovir and an indication.
DR. GREENBERG: Yes. Thanks. Thanks, Dr. Kimberlin. I -- we, you know, had engaged with you to find out everything that you had gone through

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and to see whether -- because PTN has this special pathway by which we can pursue changes to drug labels outside of the -- the industry space; right? So we have this -- this way to engage with FDA and introduce these label changes.
But I think we encountered the same barriers that -- that you had, and that's where I brought up those -- the -- you know, the issues of previous studies, although totally agree with you from a clinical standpoint, and almost all neonatologists, I think, are in agreement that for moderate to severe congenital CMV, that there's a -- that there's a net benefit to -- to treatment, and that's why you see everyone being treated.
Although, there -- you know, there is no indication. And there -- there seem to be an insurmountable barrier for us to be able to -- to use just existing data to help pursue a regulatory change.
Now, we -- we did -- we did have a lot of -- we did have other discussions regarding how real-world data might help to add to the body of evidence and would -- better preliminary, I guess,

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signals from a regulatory standpoint were that it was going to be hard to get to the level of evidence that was needed, which is sort of that well controlled efficacy trial.
So we just kind of ended up in a standstill. That's where we started pivoting, you know, our focus to maybe -- maybe postnatally acquired CMV; there's something we can -- we can do there.
But it still leaves us just with a bad stuck feeling of, you know, how -- how is, you know -- how is the entire clinical community that takes care of these infants and parents kind of on one -- in one place and a agency at the -- in a different place.
But I understand the -- the perspective as well. So --
DR. PICA: Thank you, Dr. Kimberlin and Dr. Greenberg. Dr. Bo, just briefly, and then we'll go to break. Thank you.
DR. BO: Yes, very briefly. I think the lack of feasibility is a back breaker for pharmaceutical companies trying to invest in developing drugs.

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And I think what the Pediatric Trial Network and what you're doing, Dr. Greenberg and advising others, is really amazing.
Yet, I also wanted to quickly add to the question for which we can think about later following the meeting, which is how can we incorporate data digital and new technology that seems to connect us all over the world?
You know, with the -- with this technology, how can that -- how can that be leveraged further to try to connect with underserved communities, to try to connect with rural communities across the U.S. -- across the world, have better access to clinical trials, which are needed to enhance the feasibility, therefore, bring new drugs into the market?
And we often -- I can tell you that the experience of running different clinical trials is the lack of feasibility and when we hear about patients who have a condition that will qualify for the study.
Yet we also hear at the same time, well, that they're not part of the study; they're not

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even close to a participating trial center, and our hearts and -- and stomachs are wrenched about not being able to provide access, just simply because there isn't -- there's a major gap between data digital and technology, allowing for the satellite sites, you know, for these mechanisms to offer the extension of the study to those underserved communities.

DR. GREENBERG: So really, that's a really great point, and I think, you know, the complexity of the types of studies that need to be done under regulatory guidance, you know, does limit, you know, in some ways how -- how many -- how many sites can engage.

It's -- there's a cost barrier. There's a -- a, you know, ability and experience barrier. But, you know, I think opening our minds to other types of studies and what kind of data could be used to support labeling, indications, post marketing evidence is -- is really key.

So thinking about what -- can we take advantage of, you know, maybe not -- maybe not totally

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retrospective EHR data, but sort of a registry format, or a lot of the -- a good number of the studies we do in PTN are opportunistic. So, you know, you saw all the sites on our -- on our map.

Many of them are participating in studies where the children -- children and infants are involved when they're receiving these medications. But as part of standard care, they're not enrolled as an intervention. They're enrolled -- so it's a simpler study.

It's more of a data collection and maybe some by a specimen collection, which does require expertise as well.

But there's -- there may be ways to think about what kind of study design, and that would probably take us into the next hours as well. Would --

DR. CONCATO: Yeah, we're -- we're going to break. But if I could just slip in for the record --

DR. GREENBERG: Yeah.

DR. CONCATO: -- that Dr. Bo's

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question, the FDA has published a guidance on decentralized clinical trials.

I'm not suggesting that this current context is amenable. But I think we'll pick up after the break with a lot of these issues, likewise, to Dr. Greenberg.

It's not that we are slamming the door on other avenues, other approaches, but it's -- the devil is in the details.

So thank you.

DR. PICA: Thank you, everyone. Wonderful discussion. I hate to -- to cut it short. But we do want to make sure we get at least a brief break in here. So we will -- we will take a quick break and meet back at 2:15. Thank you, everyone.

(Off the record.)

DR. HODOWANEC: All right. Welcome back from break, everyone. We will now begin our final session of the workshop. Hard to believe it's coming to an end.

So for this second half of our congenital CMV panel discussion, we would like to talk

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about various clinical trial design considerations. And we've sort of broken it up into three distinct topics acknowledging that these all sort of blur together, and -- and it may just be one large conversation here.

But we wanted to focus on study population, appropriate efficacy end points, and -- and potential comparator treatment groups.

And so we'll start again with the -- with the ideal study population for clinical trial enrollment, but again, sort of acknowledging that this may all bleed together.

So what thoughts do people have on sort of what makes sense in the current landscape regarding study design population, be it -- again, this is sort of the old terminology, I guess, now. But symptomatic versus isolated hearing loss versus asymptomatic or some combination thereof.

I can't see the -- this group is being uncharacteristically quiet. Anybody want to take the first step? Dr. Bo, go ahead.

DR. BO: Maybe, actually, I'll break

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the ice a little bit.
And, David, I -- I love that you raised your hand, because you've done a couple of landmark studies in -- in this area.
And maybe I -- if I can frame the question in a way, maybe it -- it could help contribute a little bit further here on this question about the ideal study patient population and clinical trial enrollment in order to produce data that is going to be meaningful and essentially help to improve patient outcomes further, which is, based on your experience, David, with the two completed trials and I think a lot of what we've sort of discussed and learned throughout today.
If you had to do it over again or -- or knowing what you know, what would you do differently around -- in order to -- to have the fastest and most effective way to produce data that could influence a practice among a patient population that has such dire needs, David?
DR. HODOWANEC: Excellent questions, Dr. Bo.

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Dr. Kimberlin?
DR. KIMBERLIN: Well, that's a good question. I -- I don't know that I -- I don't know that the -- the basic study designs would have been different, even with -- with retrospective eyeglasses on.
Certainly, the -- the follow-up would have -- we would have been much more diligent with the follow-up of the first study, the -- the IV ganciclovir versus no treatment randomized trial.
That was our first real foray into the population and -- and it -- there are real challenges in studying congenital CMV.
I think that for -- for -- well, I'll say -- I'll say this. One of the -- one of the things is asymptomatic. We tried to do an asymptomatic treatment study, and nobody wanted to be involved in it.
It -- it -- we ended up having some toxicity issues as well. But the accrual was, to be honest -- it just wasn't -- it wasn't going to complete.

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And then the -- the safety issues came up. So that was the -- the reason for shutting down the trial.
But what we found is that when a baby looks -- at least this is my interpretation of it, when the baby looks normal and you tell the parents who have never heard of CMV and they have this brand-new baby that the baby is infected, first of all, it takes a while to process that.
And secondly, then you say, "Well, there -- and there's an 85 plus percent chance that she's -- the baby is going to be fine, and we want to give this drug for X number of months, are you interested in doing that?" And most of them said, "No, thank you."
So -- so I think the asymptomatic population, unless we identify a way to enrich it with a biomarker that -- where we can -- we can be more assured that a particular baby is more likely to have hearing loss than just the general population of asymptomatic congenital CMV babies, I don't -- I don't see that as a population we can -- we can focus on.

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I think, you know, some -- hearing loss only, symptomatic, I mean, I -- I think we do have to keep in mind that the antivirals we've seen the data for, the antiviral drugs are -- valganciclovir is being used. I think we have to keep that in mind if we try to do a -- a placebo control in those populations. I don't think it would be -- I don't think anybody would sign up for it there either.
I think for the next big advance, I would -- I would look toward combination antiviral therapy in populations already recommended to receive antiviral treatment.
I would try to look at biomarker development. Although, you know, that -- that could -- we might have to wait five years to get those data, or they may never become available.
So I'm not sure we should wait for that. But that's where I see things really -- really developing next, in my -- in my consideration.
DR. VISWANATHAN: Thank you for those comments, Mr. Kimberlin. I have a quick -- and this is Prabha again. I have a quick follow-up question

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for you.

You mention the difficulties with accrual in the asymptomatic study. I'm curious whether we -- we have a more -- a conversation that's agnostic to the drug under study and then perhaps there was one with a very clean safety profile, do you think that -- that would be different?

DR. KIMBERLIN: So with -- so in other words, with a different safety profile?

DR. VISWANATHAN: A drug that perhaps would need less laboratory monitoring, whether those were factors, I guess, is my question.

Is -- is it the monitoring? Is it simply the knowledge that probably your baby is going to be fine and -- and that this -- nothing is needed at all? I'm just curious if you could dig into that a little bit more.

DR. KIMBERLIN: Yeah. I'm only guessing. Because those that turned us down, we don't collect data on, because they turned us down, and we -- you know, we can't -- we can't do anything with respect to -- to analyzing reasons, because they

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didn't sign the consent form.

So my speculation though -- my observation is that they just didn't -- they just weren't interested. It -- it wasn't so much the toxicity of the drug, it might have been the duration.

We -- we were proposing to treat for four months. And that might have been off-putting. So let's say you had a drug where you could give a single shot, and it would -- IM injection, and it would -- it would last -- it would do everything you needed for it to do. That might be a different matter.

But asking a family -- my experience was asking a family who was -- who was just completely blindsided by any of this, to -- to treat for at least a longer period of time -- it wasn't so much the toxicity of the drug -- I think for most of them, it might have been for a few, but it was more just, "I don't want to hear that. My baby is fine. Look at him. Everything is good." And so I think that was more what it was.

Now, could education of CMV -- again,

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this would take a decade or two to do, but could we -- could we have better education about CMV, so it's -- they're not hearing about it two days after delivery when the -- when the test comes back positive maybe.

But -- but again, that's not an immediate fix for us, in terms of how do we move this field forward now.

DR. HODOWANEC: Thank you, Dr. Kimberlin.

If we could shift just slightly back to the isolated hearing loss population, you know, sort of putting aside the issues of a comparator and whether this would be an add-on to standard of care study or those sorts of questions.

You know, I'm wondering if Dr. Schleiss or anyone else would like to comment on sort of the feasibility of enrolling that isolated hearing loss population or challenges generally in that population, given sort of the current variable screening practices?

DR. SCHLEISS: Yeah, I mean, I would comment on -- on that in the context of Dr. Albert

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Park's study throughout the University of Utah, a really beautifully designed trial that was going to try to -- to answer the question of whether isolated sensorineural hearing loss is something that should be treated with antiviral therapy, good controls, well designed.

Enrollment was just impossible. It was really difficult, and that study just simply couldn't enroll enough babies to continue. So for some of the reasons David brought up, I think future trials like this are going to be really -- really very challenging.

Now, with respect to, you know, the universal screening, I -- I mean, that creates a whole set of challenges in my mind, because all of -- all we know, really, about antivirals in congenital CMV is from babies that are identified in the context of clinical care; right?

There's -- there's something about this baby that prompts an -- an evaluation or workup, whether it's a failed newborn hearing screen or some other clinical finding, and now, we have all of these

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babies who are -- are found by universal screening where clinicians would not have thought to look.

And now, Megan Pesch has pointed out quite eloquently in some of her writings and comments that clinicians do overlook the obvious sometimes, and that's another argument in favor of universal screening -- babies that really should have been picked up by a clinical acumen are -- are missed.

But let's face it, most of these babies are asymptomatic. And so we do these evaluations. We do these workups. And we find all of these incidental findings that may or may not be important.

And -- and what -- what, indeed, do we make of this finding of a -- of a subependymal cyst? What do we make of this finding of leukostriate [sic] vasculopathy? We pigeonhole these babies into symptomatic categories.

But we need to recognize that all of those categories were developed through workup and evaluation and assessment of -- of babies who identified in the course of clinical care as needing an evaluation for congenital CMV.

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So I guess I would argue we really need very -- very rigorous studies of -- of these asymptomatic babies identified by universal screening.

And -- and as I pointed out this morning, I mean, maybe -- maybe the argument can be made that newborn screening programs really shouldn't be the focus of where these evaluations are being done. Maybe they should be being done under the leadership of any programs.

I don't know. But I -- I mean, I think we're doing good. I think we're -- I think we're helping babies by doing universal screening. But -- but there are a lot of challenges, and it's -- it's going to be really hard to sort -- sort these asymptomatic babies out.

DR. PICA: Thank you. Thank you for that, Dr. Schleiss.

I think to take this a step further, well, what about, you know, the infants who were asymptomatic at birth and then over, you know, the -- the first several months of life are diagnosed, and -- and you start to realize that they are having some

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hearing loss, and -- and that there is at least some degree of symptomatology there, is there a role for clinical trials for those patients? Is there a timepoint beyond which we -- we don't think that it's -- it's appropriate to be considering antiviral therapies anymore.

Any thoughts on sort of these slightly later diagnoses where we still think it's congenital infection. But they're a little bit beyond the normal window for when you would be considering starting antiviral therapy under the current paradigm?

DR. KIMBERLIN: Well, I'll -- I'll jump in. I hope Paul Griffiths can -- can follow with -- with additional information.

But he alluded, I think, earlier to a study that we did called the "Valgan Toddler" study, and I think it was on one of the slides too. It was published earlier this year in the Journal of Pediatrics.

And -- and in that study, we enrolled 1-month to 4-year-of-age subjects. We intended for it to be, overwhelmingly, exactly the population that you

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mentioned, somebody who -- who was normal at birth, wasn't even tested for CMV most likely, developed sensorineural hearing loss.

We go back and pull the -- they sign informed consent; we go back and pull the dried blood spot. They're PCR positive. Setting aside the sensitivity of the dried blood spot, the specificity would rule in congenital CMV, and then we randomize to either six weeks of oral valgan or a placebo.

And we -- we enrolled -- took a while to do it, because all these studies do, but we enrolled the -- the study, and we saw no difference whatsoever. Now, in retrospect, looking at the population we actually enrolled, it was very heterogenous.

It was -- we had -- we had more symptomatics at delivery than assymptomatics at delivery; that they had been treated initially, but -- you know, so I -- I tend to think that probably is either -- either it didn't work or we just -- our population wasn't one that could have -- that could determine whether it works.

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But nevertheless, it was -- it was a negative study. Now, you contrast that with the -- the CONCERT study from the Netherlands that was mentioned, and what -- and that was really the basis of the American Academy of Pediatrics Committee on Infectious Disease's recommendation recently to -- to treat isolated sensorineural hearing loss.

And they did -- they --theirs was not a controlled study. But it -- but they did some really nice statistical analysis, and they found a benefit.

Now, in that study, they were very rigid about not enrolling beyond 12 weeks, 6 days following delivery. So up to 13 weeks is -- I think Mark Schleiss mentioned in his talk. So I think that -- and that's the reason, again, that the Red Book Committee loosened up the time the drug could be initiated -- started.

But I think you'd have to say right now, beyond 13 weeks -- 13 weeks, 0 days, the data, if anything, would say it doesn't work. So, Paul, let's here what you have to say about that.

DR. GRIFFITHS: Well -- well, I agree,

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David, with that analysis. And I just wonder if we should tie this in with Dr. Pesch's talk -- her second talk where she argued that perhaps we should move away from this classification of -- into symptomatics and asymptomatics.

Perhaps we should have randomized controlled trials designed to recruit patients who present it certain ways to the medical system.

So those who were born in a hospital and have symptoms and are worked up and found to have congenital CMV that can be called "symptomatics," and that's kind of the same as normal.

But those who don't have a clear signal on their hearing screening test are probably a different group. They're all in the first few weeks of life, and then perhaps reasonably, homogeneous.

The other ones who present, they're quite -- quite different; aren't they? Perhaps they should be recruited into a different study. Perhaps they should be on means of presentation that leads you to have a classification.

And as for the asymptomatics, I accept

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that there would be lots of people who don't want to go into trials. But the -- if you started national screening in the whole United States, then there would be enormous numbers coming through, and some parents might want some action taken, as long as at the time you ask them, "Are you prepared to be randomized to drug versus placebo?" And if they say, "Yes," then they could be recruited at that particular time.

DR. PICA: Thank you, Dr. Griffiths. Anyone else have any thoughts regarding population that they would like to share, any follow-up questions?

All right. Then let's move on to talk about end points. And again, we've sort of already started down this discussion path. And, you know, we talked a lot about various hearing related end points. But we've also heard that -- that might not be the most meaningful end point to -- to patients and parents.

So I -- I'd love to hear the -- the panel's thoughts on that, hearing versus other longer term, other neurodevelopmental outcomes, from both a

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meaningfulness perspective and then also balancing that with a feasibility perspective.

I know we've heard a lot about how challenging these long follow-up periods are to implement. So I'd like to hear the panel's thoughts on -- on these potential clinical end points.

Dr. Pesch, please go ahead.

DR. PESCH: Thanks. I'm -- I'm driving my daughter home from school right now. This is -- so I hope my audio is okay.

You know, as much as I said that I don't think hearing loss is the most important thing to families. It is a relatively clean outcome to measure and present relatively early.

I especially appreciate Dr. Kimberlin's point about the five-year grant cycle and how quickly you kind of need that data.

So many more of these perhaps nuanced developmental outcomes, you know, may require a decade to -- to measure, and I would also say are a lot more expensive to measure longitudinally than, you know, hearing in the neonatal period. So it -- it is

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tricky.
DR. HODOWANEC: Thank you, Dr. Pesch. Yes. I mean, it seems that perhaps measuring hearing in the short-term, but continuing to follow these patients, if possible, to get those longer term outcomes would be really the ideal path, I think.
Sticking with the hearing-related end points, I -- I'd be curious to see what -- what people think, you know -- particularly, hearing more from our -- from our audiology and -- and ENT analysists, if they have additional comments on this.
But sort of what -- what makes the most sense to look at here in terms of best ear, worst ear, total ear? It seems, like, depending on which of those you choose, you -- you could have very different results.
And -- and so how do we -- you know, as -- as I think Dr. DeVries had outlined, there's sort of pros and cons to each of those approaches to measuring hearing. But -- but how do we move forward with potentially designing a clinical trial and selecting a primary end point in a timepoint in which

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that primary end point is -- Dr. Kimberlin?
DR. KIMBERLIN: Well, the -- the benefit of total ear is -- is it doubles your sample size in terms of the numbers of people enrolled, because everybody has two ears. And -- and given the -- the challenges with these studies, that, I think, can be helpful. So -- so that -- that would be point number 1.
And then trying -- I think trying to protect hearing -- now, that's not to say -- you know, protecting normal hearing would be great and should be part of it. But also protecting, you know, if you have moderate hearing loss and -- and that gets protected, that's good too, or at least it's meaningful as well.
So I think -- I think protecting what you got, rather than seeking to improve, is probably more realistic with -- at least with the drugs and the understanding of the disease that we have right now.
And then I would -- I would come back to a point I tried to make rather inarticulately yesterday, I think. I -- I really think for these

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rare diseases, we need a primary end point, because you got to have a primary end point.
But -- but things shouldn't be judged just on the primary end point. We should be looking at the full story that's being told across a given study and across multiple studies to see what the totality of the indication is with respect to whether it works or not.
And it's not perfectly clean. It's not as pristine as -- as, you know, enrolling 50,000 people and hitting your primary end point. I understand that.
But I think it's the reality of these rare disease, at least rare infectious disease, situations that we're -- we're trying to have -- move the needle on and make things better.
DR. HODOWANEC: Thank you, Dr. Kimberlin. We -- we hear you, and -- and we do, you know -- we definitely support the idea of looking at the -- the totality of the data. But we do also need, you know, persuasive data at the end of the day.
I will now call on Dr. Griffiths.

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DR. GRIFFITHS: So looking at your request to focus on real-world data, could we have primary end points as did the child need a hearing aid; did the child need cochlear implants; did they need to have special arrangements for their schooling because of their hearing problem?
Could those be worked up into a composite, so perhaps those who didn't need any of those interventions versus those who needed one of them? Because of course, they may overlap, and they have more than -- more than one.
Should we be trying to look for real-world data that -- that makes sense to patients and their parents?
DR. HODOWANEC: I see that Dr. Pesch had her hand raised, and I will come to you in one moment. But I also -- I'm first going to turn to Dr. John Concato who may have some comments on -- on the feasibility of using real-world evidence for -- for those type of data collection, those types of end points.
DR. CONCATO: Yeah. Just as there were

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issues this morning of terminology for CMV itself, I think there's issues in terminology of real-world data -- and it's nothing -- no one said anything wrong.

But what I heard actually, we're still talking about a traditional randomized trial. We're just talking about changing the outcome, the end point, and we've looked for something that tells us how the patient feels, functions, or survives.

So I don't have a problem, quote/unquote, "wearing my real-world evidence hat," or "real-world data." I'm talking about -- I think we're still on part of the landscape where we're talking about doing a clinical trial.

So I would probably go back to the division and say, you know, "What's your thinking?" We're not talking about any drug right now. But -- so I think when I -- I hear "real-world data," "real-world evidence," I -- I pause to ask what the source of data would be and what the study design would be if it's -- if that's helpful.

Thank you.

DR. HODOWANEC: Thank you, Dr. Concato.

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And if I could just follow up on Dr. Griffiths' question, you know, I -- I think that the idea of a composite end point, like you proposed, I think that that's -- I think that's an interesting idea that -- that we certainly should consider.

I'm curious from the clinicians, what is the timeframe typically -- and I'm sure this is variable, but for -- for those children who have congenital CMV infection? What is the typical timeframe with which a cochlear implant might be needed?

UNIDENTIFIED SPEAKER: And is there even consistency --

DR. PESCH: I can answer --

DR. HODOWANEC: Oh, thank you. Sorry. Thank you. Yes, please, Dr. Pesch.

DR. PESCH: Yeah, I can answer that. So at least in the U.S., if it's congenital, like, from birth, hearing loss in a severe to profound range, nine months is when -- right now, cochlear implants are occurring.

Although, for bilateral, I should say,

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that's kind of the lower threshold, unilateral. There's somewhat less of an urgency.

So maybe closer to 12 months this -- you know, it's gone down even since my daughter had her cochlear implants, which was not too long ago, so previously 12 months. So I -- I -- does that answer the first question?

DR. HODOWANEC: Yes. Thank you. That's very interesting -- appreciated how early that can be.

DR. PESCH: Yeah. And I guess the other -- the point I -- I just wanted to make is kind of just to embellish off a point that Dr. Griffiths and Dr. Kimberlin made was that even -- so looking at hearing loss progression, but also the timing of that progression, every month that hearing -- prelingual access to sound can be preserved -- even if the end point is profound hearing loss, if that profound hearing loss occurs when the child is 18 months versus 6 months, the difference in terms of cognitive develop and language develop -- development, assuming, you know, that child has hearing parents and the child,

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you know, likely doesn't have access to sign language is -- is -- it's really -- it can really make a huge difference.

So not only the end points, but also kind of the trajectory of that, how -- the -- the decrease in the hearing loss progression.

DR. HODOWANEC: Thank you, very much, Dr. Pesch. Appreciate those perspectives. We have a comment in the QR -- I guess a question in the Q&A from Dr. Shannon Ross.

"Could anyone comment on vestibular dysfunction? There's increasing data that this affects children with congenital CMV with and without hearing loss and can impact motor development."

I don't know if Dr. Pesch or anyone else has any insight on that -- that they would like to share.

DR. PESCH: Sure, I can address that. Yeah, absolutely, and we're seeing it in children -- and, like you said, Dr. Ross, without hearing loss as well.

In my clinical experience, I almost see

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it always go hand in hand with hearing loss, and I think that is a big part of the gross motor delays, like the softer gross motor delays that we see in these kids, because they -- you know, as toddlers, the world goes "whoosh" when they move their heads, and so it's that fear almost of taking steps.

I think we're learning more and more about the potential of vestibular rehab in that optimal window between 4 and 8 years of age.

I think there is a study going on now, a multi-institutional collaboration, looking at some more data from these kids with CMV and pre- and post-cochlear implant, because that's another thing that might impact vestibular function. So I think it's a really hot area and more to be learned soon.

DR. HODOWANEC: Thank you, so much, for -- for sharing all those perspectives, Dr. Pesch, and I -- I have another follow-up for you. But for anybody else who -- who wants to take this.

So I'm -- I'm hearing you say the maintenance of hearing -- the preservation of hearing through that sensitive period of -- of speech and

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language development is critical. I think I heard the same from Dr. Kimberlin.

So perhaps, I mean, in my mind, I'm envisioning sort of a flat audiogram that doesn't change or doesn't deteriorate over time. Is the end point then that we'd be looking at really that audiogram and the preservation of hearing, or is it really what comes as the consequences of that?

Is it the speech and language acquisition? Is it other developmental milestones? And I know these are -- these are challenging end points to measure. But I just would like to hear your thoughts about that.

DR. PESCH: I feel, like, I'm hogging the show here -- hogging the spotlight. I'll just say really quickly, they're kind of, you know, two separate things, I think, you know, language and communication measured functionally.

You know, if a child has access to, you know, sign language, I know it's -- it's very different than spoken language in terms of -- except, like, how widely spread and available it is, but that

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can be a functional measure -- or functional form of language and communication for a child, so -- which is, of course, different than -- than measuring, you know, the hearing loss.

So I think -- I don't really know if you can say one is more important than the other. I think it would be good to measure all communication in language, because we do -- are seeing more multi-modal communications from these kiddos that can be somewhat functional. So I -- I'm going to -- I'm going to play for both teams and say both.

DR. HODOWANEC: Fair enough. They -- they both sound, like, they could be meaningful end points. And you're not at all hogging the discussion here. We -- we very much appreciate the sort of unique perspective that you bring to this discussion, and we certainly, obviously, welcome others to chime in as well.

But while we have you, Dr. Pesch, one other follow-up question we had, so if in some of the parent groups that you're part of -- trying to get a sense of sort of how the excused or what the

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proportions are for those who have maybe more, you know, just isolated hearing loss versus more symptomatic cases of congenital CMV infection, is it a pretty even mix?

Could you just tell us a little bit about sort of the -- the makeup of -- of the groups that -- that you work with?

DR. PESCH: Yeah. Yeah, absolutely. So I tend to see probably a pretty even distribution in terms of who we would think would be getting diagnosed, you know, because knowing that children with symptomatic CMV in the absence of a screening program would be getting diagnosed more often.

So I'd say it's probably, like, a 50/50 split early on, so in the infancy period. But then the families with kids who have unilateral hearing loss or isolated hearing loss, I think they tend to make their way to other groups.

Like, there's some really robust parent support groups for children with hearing loss. And it's the families with the kids who are either more symptomatic or, like, thought were asymptomatic at

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birth, but perhaps have some evolving behavioral difficulties, those are the ones that really stick around.

And we see the posts from older -- parents of older kids are primarily from this -- this symptomatic group.

DR. HODOWANEC: Thank you, Dr. Pesch.

Roberta, we're wondering -- sorry. Dr. DeBiasi, we're wondering if -- if you would like to share sort of your perspectives based on your patient panel, you know, what -- what you think would be meaningful to your patients in terms of some of these various end points that we've talked about.

I'd be curious also to hear your thoughts on -- on the composite end point or example of a composite end point that Dr. Griffiths put out.

DR. DEBIASI: Yeah. I mean, I -- I concur with Dr. Pesch that the hearing is important to evaluate, but is not the primary thing that our patients are worried about.

They are really worried about the MRI, the findings, and the cysts, and the white matter

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changes, and what does that mean, and is their child going to be able to go to school normally, and, you know, those sort of things.

So if we could become more focused on some of those end points using more quantitative correlates of that, I think that would be useful. So, you know, those would be my general thoughts.

Of course, the hearing is extremely important. But I really do think if we focus only on that or mostly on that, we're not really focusing on what families are worried about.

DR. HODOWANEC: Thank you, Dr. DeBiasi. And, Dr. Kimberlin, do you have a similar experience with your -- your patients or anything different to -- to note?

DR. KIMBERLIN: I don't know that I would have the same experience. I mean, certainly, neurologic is important. But I think it depends on -- on sort of who you're having the conversation with.

If it's a child who is microcephalic and -- and overtly symptomatic to use that

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terminology, then -- then yes, I think they're going to be more worried about it.

If it's somebody that failed their newborn hearing screen and they're just learning about CMV for the first time as they get tested and -- and then follow-up, they're going to be worried about hearing.

So I -- I think it depends on -- on what subset of the population we're talking about, and I think you got to recognize that the larger subset is going to have isolated hearing loss.

So -- so they're going to be less -- less severely affected at the outset than -- than the population that -- that would have -- be more likely to have neurologic sequelae as a consequence.

So longwinded way to say, I -- I follow what's being said; I'm not sure I would say that's been my experience.

DR. DEBIASI: I just -- just to embellish on what I -- I mean, you know, the kids that are severely affected and have microcephaly and polymicrogyria, you know, that's a matter of

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explaining to the family that those things are unlikely to be reversible and have a bad outcome.

But it's all these other middle of the road things that I think people really -- we don't know what to tell them. They're very worried about it.

And that can still include, "What does that mean for hearing?" But maybe better ways to follow these changes serially and correlate them with other things, like these biomarkers that you're talking about. I think that would be helpful.

DR. PICA: Thank you, Dr. DeBiasi. Any additional thoughts or comments regarding end points before we move on to the final topic?

Okay. With that, I will move on to -- to I think one of -- not that they're not all challenging, but one of the most challenging, I think, discussion points is -- is regarding trial design and -- and use of a comparator.

And I think, you know, we've heard loud and clear today that in the hearing loss population and the symptomatic population, that placebo

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controlled trials are likely not to be feasible.
And so let's talk about other potential approaches in -- in those populations, in terms of an add-on to standard of care type of trial design.
What -- what do people think is -- is a feasible way for potentially studying new therapies, given the current landscape?
DR. HODOWANEC: Go ahead, Dr. DeBiasi.
DR. DEBIASI: This may not be answering the question, or maybe I misunderstood the question. But, you know, it would be hard to not use valgan, since we have such great data that it has an effect.
So to me, anything we would do at this point would have to be adjunctive therapy, like is being done with the CPIC trial right now.
But I don't know. I'm interested to hear other people's thoughts about that. So to me, it would be most interesting to use things that we know work, plus and minus other things that we want to know if they improve -- what we already have seen for improvement.
DR. VISWANATHAN: Thank you for that,

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Dr. DeBiasi. And so what I'm hearing there is -- so there is -- they're studying valganciclovir, plus or minus adjunctive therapies.
What if it was a novel antiviral? How -- how would you see that being incorporated into the -- into the clinical trial design?
DR. DEBIASI: Well, I think it would be hard for me to enroll people if you mean only the novel antiviral versus something that we've already studied and know has an effect. So that -- that would be my point.
DR. VISWANATHAN: We recognize also that the -- the answer to this question depends on the population understudy and -- and those -- the certain population where there might be more equipoise about whether antivirals are affected.
We would love to hear your thoughts in any population -- if -- if there's any clarity in anyone's mind about a population in which it would be clear what the design would be.
The silence is very informative, indeed.

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DR. DEBIASI: Well, I think clear is hard for this whole area. I mean, obviously, nothing is clear. But if we're going to continue to focus on the hearing loss, it makes sense to me that we build on what we already have, like is being done. But the idea is, are there other things that could be looked at, besides letermovir.
Should we be using adjunctive anti-inflammatory therapies as another choice, or should you be using some other antiviral in addition to valgan? But that would be my thought.
DR. GREENBERG: I think the challenge for new drug development -- and, you know, others can please fell free to weigh in, but, you know, if your comparator is -- is valgan, you know, you might -- if you -- if you propose to have a safer therapy than -- than valgan, then you have to do -- you still have to have a superiority trial.
You can't win with a noninferiority trial in a safer medication, because valgan, in the eyes of the -- right in the eyes of the regulatory authority is not, you know, indicated for this

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population.
So I think, you know, it becomes a real challenge for developing new things, even if you try to use valgan as a comparator.
DR. HODOWANEC: Does anyone have any comments on duration of therapy and -- and sort of how competent people are that -- that six months is -- is the right duration -- optimal duration?
I don't know if -- you know, I think it depends on the -- they type of therapy. But, you know, for -- for antivirals in particular, how confident are we that six months is enough?
Would there be different outcomes if we studied -- continued an antiviral therapy for -- for a longer duration or if we had, you know, a more -- a drug that could be tolerated and potentially administered for longer, given that, you know, we've heard that these hearing outcomes are really evolving over many years, not just the first six months or -- or so of life.
Well, I'm sure David has thought about this a lot. We're waiting to hear what he would say

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about it. But I can just tell you, the families are very happy to stop at six months. They are marking it on their calendar and very happy when it's over.

So, you know, selling it for longer I think will be harder. But -- but there's certainly reasons why if you follow the logic of the studies that have been done so far, why treating longer would be maybe a good idea, if it's ongoing viral that -- that we're looking for, which we just said we don't know. So that's the tricky part.

DR. KIMBERLIN: Yeah, I think I -- I've had the same experience where -- where they're happy when they get to the -- the finish line of six months.

I'll say that we could entertain a three-year-treatment course. We can't get it funded to study it, because there's not enough time to treat for -- to write the protocol to treat for three years and to follow to know.

So to some extent, we can hypothesize all we want. We're going to run up -- at least I believe we're going to run up against the reality of what can get done.

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DR. SCHLEISS: Yeah, I -- I mean, every family is different. I -- I agree with Roberta. Most families are quite happy to reach the finish line.

But I've had a few families that want to go longer. I've had, you know, some families tell me that -- in various chatrooms and Facebook groups, that they know some clinicians who are treating for a year, and that -- that makes me nervous without any data to support it.

But it just kind of underscores that, you know, there's a wide range of opinion about everything on the internet, I suppose.

It gets back to what I was talking about a little bit earlier too in terms of the longer you suppress replication, the less likely you will to develop a protective T-cell response, perhaps.

And I still think that that's something we need to look at in terms of the impact of long courses of antivirals on eventual T-cell control. Although, the -- the paper from the Spanish group that I referenced earlier suggests that -- that doesn't seem to correlate with sequelae.

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DR. PICA: Thank you, Dr. Schleiss. I know there's been a lot of interest in looking at the T-cell -- you know, CMV-specific T-cell responses in the transplant setting and -- and sort of along those same lines, thinking that long periods of -- of drug exposure of prophylaxis could ultimately just sort of delay the -- the natural immune response and could have some potential negative impacts.

But yes, I think it seems, like, there's a lot unknown about that in the congenital CMV space. But that's a great point.

Dr. Kimberlin?

DR. KIMBERLIN: A couple of points. Mitch Cairo has a study that's starting soon using CTLs in congenital CMV up in New York, and so that's one to keep an eye on. And -- boy, that was -- so that popped in my head, and I blanked on what else I was going to -- oh, I know what it was.

The idea of -- the talk earlier about different ways to administer a drug was interesting to me. You know, ocular ganciclovir implants -- I looked it up during the talk, because I didn't know how big

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they were, they're 4 millimeters in diameter.

I have no idea how much space there is in the middle ear of a -- of an infant. But -- but could a -- could an implant delivering drug locally, assuming it crosses into the inner ear, could that be a way to have sort of a one-time intervention with a longer duration of potential treatment effect? I don't know.

DR. HODOWANEC: Thank you, Dr. Kimberlin. We -- we were -- we were similarly intrigued by this possibility of -- of a more local administration and whether there could be some sort of extended release at -- at the site of -- of concern.

I don't know if -- if Dr. Kau is on the -- on the call. If have -- you have any additional comments, we'd love to hear.

DR. KAU: Yeah. I think --

DR. HODOWANEC: Go ahead.

DR. KAU: Oh, sorry.

DR. HODOWANEC: Go ahead.

DR. KAU: I think the idea of putting -- that's an interesting idea. I don't -- I

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don't -- you know, there is issues with anything going into the middle ear, because that in and of itself can cause some conductive loss just by being there.

You know, I probably don't know the exact size of a neonate, but -- middle ear space, but it's interesting. I think if you could find a way to do something like that where it wouldn't interfere, perhaps you can get some exposure to round window. But I would -- I would think it would have to be quite small.

DR. KIMBERLIN: Yeah, I -- I would just point out that Dan -- I helped Dan Choo at Cincinnati Children's write an RO1 some years ago, which we looked at -- at a preclinical model in guinea pigs to ask this very question, inspired, in part, by some of the interocular ganciclovir data that goes all the way back to the pre-heart -- the therapy era and HIV patients.

There was a time in the, you know, late '80s, early '90s that interocular ganciclovir was -- was not, you know -- was -- was used actually fairly often.

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And there was another drug, fomivirsen, that was approved for intraocular inoculation for HIV-infected patients with CMV retinitis. I don't think that's on the market anymore.

But anyway, Dan and I tried to pilot this in guinea pigs. Part of the problem was that the guinea pigs' cytomegalovirus is intrinsically resistant to ganciclovir, so we could never really do efficacy studies in the animal model.

But I was glad to hear that talk earlier today, because it is something I know Dan is still interested in at Cincinnati. And that would -- I mean, wouldn't that be great if you had a long-lasting antiviral implant, and it actually worked, and you could avoid the systemic toxicities of ganciclovir?

So I think intratympanic injection -- not a new idea, but one that we certainly need to continue to think about, and maybe we can find a way to dust off the guinea pig model and find -- find some other strategy or some other antiviral to revisit that question or even the rhesus macaque model.

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I don't know if -- if that's been looked at in that model or not -- antivirals. I don't know if Emma is still on the -- on the call. She -- she might -- might know that literature.

But it's a great idea. Would be great to see some local delivery techniques for CMV inner-ear disease.

DR. HODOWANEC: Yeah. Thank you for all of those comments. I wanted to acknowledge Dr. Abzug's comment as well that this is given that the -- the drug itself would not be cytotoxic in and of itself if administered through this route.

But we did think it was kind of a provocative idea, especially for those children where that duration of therapy is not really well known. We know that there's both pragmatic challenges to prolonged systemic therapy, as well as the side effects of -- of that exposure.

And so if you have a child, a toddler perhaps, with tympanostomy tubes, you could inject via that tube for local therapy. Something just -- food for thought.

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And, Dr. Griffiths, I see that you have a comment to make.

DR. GRIFFITHS: Yes, I was just going to get back to the question -- somebody said, "Does the antiviral drug suppress immune responses?" And there's evidence from a solid organ transplant in a randomized controlled trial, seronegative individuals randomized to valganciclovir prophylaxis or ganciclovir given preemptively.

And preemptive was superior to prophylaxis in terms of preventing late onset disease. And they published a paper recently showing an explanation for this.

There's blood -- or blunted CD4, CD8, and antibody responses in those who receive the drug continuously, rather than intermittently and presuming the drug is potent enough to delay antigen presentation to the immune system.

That's about the only evidence I know. We have to be a bit care -- a bit careful before applying this to -- to children.

Of course, we're talking about neonates

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here that have immature immune responses. But they're not receiving immunosuppressant drugs. But they have had long antigen exposure in utero before they come to your attention. So there are quite a few differences between the two groups.

DR. PICA: Thank you, Dr. -- Dr. Griffiths. Excellent points. Any other comments on the comparator topic or any other trial design comments before we move into our -- our last discussion point here, which is sort of the sub bullet of -- of the comparator discussion looking into real-world evidence.

Okay. So I mean, we've sort of already been -- been somewhat dancing around this issue of what is the -- the rule for utilizing or leveraging real-world evidence to help advance drug development in the congenital CMV space, given all of these clinical trial pragmatic challenges?

We want to just open the floor for any additional thoughts -- comments that people might have on how you see real-world evidence potentially playing a role. And I will let Dr. John Concato start.

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DR. CONCATO: Yes. I'll admit to not answering your question, but rather, hopefully, enabling a discussion by describing briefly what might be the landscape, at least from one perspective.

Do we agree if we have a new molecular entity, you know, by definition, we don't have real-world data available? So in that case, we will think of our faced approach to trials, and we could talk about what exact, you know, trial needs to be designed.

And a second layer, there are improved drugs, say, for CMV in adults. And this is where we heard this morning from Dr. Greenberg about the PTN and how -- but that would depend on doing another trial as well.

So if we have approved drugs where "real-world data," quote/unquote, are available, but we're thinking about more -- that more generally, that's where I think the question -- that's where I might toss it back to you, Aimee, is that -- is that what you're asking about, specifically, whether we're talking about externally controlled trials or other

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design types?

Because I think it's -- there's so many moving parts. We need to be clear where exactly we are on that so-called "landscape." Does that make sense, Aimee?

DR. HODOWANEC: Thank you, Dr. Concata. Yes, it does make sense. And -- and I think we didn't necessarily have a specific potential approach to the utilization of real-world evidence in the congenital CMV space. I think we wanted to just sort of get the -- the group's thinking on this.

DR. CONCATO: And I'll just make one more point. I mean, it's a tie-back to what was mentioned earlier, and credit to Dr. Abzug for bringing it up. If we go back to the specific question, this is not about getting a new drug approved.

But if there's concern about carcinogenicity, I stand by what I said earlier, it's not easy. On the other hand, you know, we shouldn't give up on it.

So if we're looking to see whether a,

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quote/unquote, "signal" is there, that's where I'm certainly not speaking on behalf of the Critical Path Institute. But I will connect the dots between today's discussion and yesterday's for those who missed yesterday's.

One of the projects that the FDA is supporting is with the International Neonatal Consortium. Their -- the focus of the award was to look at lab values, and they have a -- they were working on a disease model for bronchopulmonary dysplasia. So it's not CMV, and again, I'm not a pediatrician or a neonatologist.

I'm not speaking for C-Path. But with 400,000 plus -- with the data on more than 400,000 plus neonates, I -- our one question might be whether it's worth giving those folks a call to see what they have and whether it -- it's a future grant, even if it's looking at the natural history, et cetera, or looking for a signal back to the -- the question of whether or not cancer is increased or not.

I know this is a somewhat of a diffused comment. But I'm just trying to help by seeing where

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we might put down a stake in the ground and -- and have some -- some anchor to start with.

So both a general comment about the landscape, as well as the specific comment about, I think -- yeah, that if the data are -- if -- if the signal is out there, we should be able to find it.

And one -- one last point, sorry for bouncing around, but I -- I would ask Dr. Greenberg to comment on PSNet. I know they're not always doing trials. But we have a separate -- one more vignette.

The FDA approved a new dosing -- loading dose for Vimpat -- lacosamide. It's not the most dramatic approval ever. But it did use "real-world data," quote/unquote, "real-world evidence" in lieu of a new trial.

Now, granted, the effectiveness side of the approval was based on extrapolation. But the real-world data were used to be comfortable with a labeling change last year in terms of the age was lowered to 1 month. I think it had been 4 years. I would have to look up the details.

But just to show that we are committed

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to -- to the appropriate use of real-world data, real-world evidence, but in each context, what RWD/RDE is differs, and at all times, we're not trying to be anything other than protecting the public health by making sure that the evidentiary standard is maintained and as has been mentioned earlier, we clearly are more flexible with rare disease, not by lowering the standard, but by understanding the context that we're in.

Thank you.

DR. HODOWANEC: Thank you, John. All very useful comments. I think when we drafted these panel discussion questions, the -- the real-world evidence question, I think we were envisioning more of a discussion about, you know, a historical control, that type of thing, given the -- the issues with having a placebo-controlled trial, given the current landscape.

But I think as has been raised over the course of today, there are other ways, such as -- as exploring potential safety signals that -- that we could consider leveraging real-world evidence.

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DR. CONCATO: Yeah. One -- one more repeat. I'll put it in the chat after I'm done speaking. But for those who weren't on the call yesterday, if there's enthusiasm to look at the feasibility of an externally controlled trial, AKA, you know, it doesn't have to be natural history, but a comparator arm from somewhere other -- essentially a single-arm trial and a comparator arm from somewhere else, then our externally controlled trial guidance is the place to look if one is thinking about a regulatory submission.

And I think we've been pleased by the fact that we're being criticized from both sides. Some saying how could we dare think of doing anything, other than traditional randomized trials, and others saying that we weren't permissive enough and not that everything should fly, but that we -- we basically say the natural history has to be understood.

I think the problem here is, it's -- it's not a very optimistic starting point. It's no one's fault, but the -- you know, the heterogeneity of the disease, the problem with identifying an outcome,

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and also the anticipated effect size, we have more confidence that bias is not going to explain an apparent dissociation.

If the apparent -- if the expected effect size is large here, I'm not really hearing about, you know, candidate drugs that are -- that are showing promise, but just haven't been vetted through, say, traditional phase 3 trial. Thank you.

DR. HODOWANEC: Thank you, again, Dr. Concato.

One sort of related comment that we have in the Q&A is "Have there been efforts in the past, or is there interest moving forward in establishing a registry capable of capturing data from routine clinical practice for infants with congenital CMV?"

Dr. Bo?

DR. BO: Yeah. I think along the lines with that question, I'm wondering -- you know, we have -- Dr. Greenberg I recall spoke about -- really greatly -- nicely about the clinical trial network. Could that network be leveraged to essentially look

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into some of these questions?
From a public health policy perspective, I think what was mentioned was that the practice of using drugs for which there isn't an official indication for, and could the network essentially capture the -- how -- how that -- the patterns of practice and outcomes associated with those -- with those practices can be qualified.
DR. GREENBERG: And this is Rachel. So we have -- I mean, we definitely explore the use of registries and other indications, and so I think that is -- is definitely -- definitely possible. I think it's in -- where we've explored has been a therapeutic area, which was not as much of a rare disease.
And so, you know, I think to -- to have a successful registry here, we'd have to -- we'd have to think about the -- the resources.
I think the PTN specifically has the mandate to affect drug labels. And so understanding the pathway by which registry data could support a change in -- in a drug label is -- would be really key.

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But I think such a network that has established sites across the country could be an ideal setting for the -- building something like this, because we have other studies going on that are more opportunistic, observational.
So, you know, if this was realized -- if it was recognized, could we -- and, you know, have, you know, a participant with -- a potential participant with congenital CMV, could we capture all of those participants at any clinical trials that I think -- thinking outside the box, that would be really exciting to -- to think about.
So -- and I think a registry would offer the opportunity to capture potentially the natural history that is -- we think is really difficult to capture.
So there, you know -- there are situations where -- in the current setting, where these patients are missed or, you know, they don't -- especially those with, you know -- it -- it's less likely, I think, in moderate to severe congenital CMV.
But it's possible. And so you could

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have -- you could capture those and -- and have maybe some comparator arm to something captured prospectively.
Dr. Pesch, it looks, like, you'd like to weigh in.
DR. HODOWANEC: Thank you, Dr. Greenberg. Yes, thank you, Dr. Greenberg.
DR. PESCH: Oh, yeah. I just wanted to mention that last year, the National CMV Foundation was awarded a grant from NORD to create a registry for CMV on their IMRARE Platform. And so it's currently being designed. I'm on the advisory board. It's not launched yet.
But they -- in terms of the design, I think, looking at natural history, as well as family impact and some of the psychosocial measures, was the initial focus of the registry. But the National CMV Foundation was -- is very open to collaborating and part of the idea behind this registry is to use it for research purposes and have it be flexible.
So if anyone wants to get in touch with me, I can loop you in.

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DR. VISWANATHAN: Thank you, to both of you, for those comments.
And I'll just share some of the work that we've been doing internally at FDA, just trying to understand from our standpoint just doing demonstration projects in the space about can you really follow patients over time; can you identify them in electronic medical records and what not?
What we have found to really be a challenge is because of the multi-disciplinary nature of this illness -- of congenital CMV, the medical record at one institution tends to be quite fragmented, because a child might receive care in -- primary care in one place, ID care in another place, ENT in one place, OT/PT outside of an insurance building system, for example, through state or other local municipal services.
And so aggregating the -- the records for each individual patient from all those different care providers is hard and, therefore, leads to a lot of missing data if you go to one -- what we believe was one central source.

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So it is -- it is a challenge, and -- and anybody who was trying to undertake building a registration, just be aware of that from the outset of how many partners you would have to have to get a full clinical picture represented.

DR. HODOWANEC: I'd like to go to another question in the Q&A. We talked a little bit about PCORI before. But we have a question, "Has anyone queried PCORnet?" Does anyone have any information on this they'd like to share with the group?

Okay. I'm going to take that silence as -- as lack of -- of information on this. And I think that's an interesting point for us to consider.

Any additional comments at this time? All right. We're hearing nothing. And I think that we can conclude this panel discussion.

I'd like to give my sincerest thanks to all of our panelists for such a wonderful, enlightening discussion. And I will now turn it over to Dr. Prabha Viswanathan, deputy director in the Office of Pediatric Therapeutics, for a few very brief

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closing remarks. Thank you, everyone.

DR. VISWANATHAN: Hello, again. It has been a really amazing two days. Obviously, this was difficult work. We knew that going into this. And we appreciate the attention, the time that you've all taken to participate in this conversation yesterday and today.

So first, let me thank all the speakers for providing very enlightening talks, setting the stage for great discussions. And thank you to our panelists who were -- have been generous with your thoughts, your opinions and ideas, which is exactly what we were looking for in this forum.

I always want to thank all of our attendees. Some of you are thought leaders in this field as well. We hope that you gain some -- some insight to take forward in your future endeavors in this space.

And to those who are new to the space, welcome to our -- to our -- our camp here. We are happy to -- to collaborate with you in the future.

I think we all knew when we convened

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this meeting that we wouldn't end -- we wouldn't depart with all the answers -- with having everything figured out. But I think we've all learned quite a bit, and this will shape our future work.

One theme that, I think, came through both yesterday and today is that collaboration is key. And I hope that this -- this conversation and -- and this conference has helped bring some people together who might be great collaborators in the future. And we would like to be part of your ten. So this is our declaration that we want to be your partner in progress in this field to get drugs for these patients who so desperately need them.

So let me just end by acknowledging a few more people. We want to thank our leadership for supporting this work in a very challenging area.

We want to thank our AV team who has been outstanding, to -- to Corey and Marcus for making this a successful and seamless event, and finally, a huge round of applause to Natalie Pica and Aimee Hodowanec who have been so generous with their time and efforts to make this a successful event.

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So with that, we will adjourn. We wish you well in all your great work and hope to see you all soon in forums such as this.

Please, don't hesitate to reach out with questions or comments. We will be updating the meeting website with materials, including slides and a transcript, hopefully in the -- in the near future. So please, be on the lookout with that -- for that.

With that, we'll say our goodbyes. Thank you, so much, everyone.

UNIDENTIFIED SPEAKER: Thank you. Thank you, so much.

DR. BO: Thank you. Thank you, very much.

DR. VISWANATHAN: Everyone. Thank you. Bye.

(Whereupon, the meeting concluded at 3:23 p.m.)

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I, ALEXANDRA HOBRECHT, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

ALEXANDRA HOBRECHT
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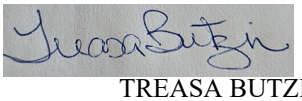

TREASA BUTZIN

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