

1 Drug Development for the Treatment of Congenital
2 Cytomegalovirus Infection and Neonatal Enterovirus
3 Infection - Day 2
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6 Moderated by Aimee Hodowanec, M.D.

7 Wednesday, May 8, 2024

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16 Reported by: Alexandra Hobrecht
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2	List of Attendees:	2
3	Mark Abzug, M.D. (by videoconference)	3 Aimee Hodowanec, M.D. 297, 364, 464, 524
4	Tien Bo, Pharm.D. (by videoconference)	4 Tatiana Lanzieri, M.D., M.P.H. 300
5	John Concato, M.D., M.S., M.P.H. (by videoconference)	5 Mark R. Schleiss, M.D. 310
6	Lindsay DeVries, Au.D., Ph.D. (by videoconference)	6 Roberta L. DeBiasi, M.D., M.S. 327
7	Roberta L. DeBiasi, M.D., M.S. (by videoconference)	7 Megan Honor Pesch, M.D., M.S. 350, 425
8	Rachel G. Greenberg, M.D., M.B., M.H.S. (by videoconference)	8 Emma Mohr, M.D., Ph.D. 374
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10	Paul Griffiths, M.D., D.Sc. (by videoconference)	10 Ryan Kau, M.D. 416
11	David W. Kimberlin, M.D. (by videoconference)	11 Rachel G. Greenberg, M.D., M.B., M.H.S. 441
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16	Emma Mohr, M.D., Ph.D. (by videoconference)	16
17	Lily (Yeruk) Mulugeta, Pharm.D. (by videoconference)	17
18	Megan Honor Pesch, M.D., M.S. (by videoconference)	18
19	Natalie Pica, M.D., Ph.D. (by videoconference)	19
20	Mark R. Schleiss, M.D. (by videoconference)	20
21	Kunyi Wu, Pharm.D. (by videoconference)	21
22	Prabha Viswanathan, M.D. (by videoconference)	22
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1	A P P E A R A N C E S (Cont'd)	1 P R O C E E D I N G S
2	Betsy Pilon, Executive Director (by videoconference)	2 DR. HODOWANEC: All right. Good
3	Corey Farley, AV Staff (by videoconference)	3 morning. And welcome to Day 2 of our workshop: Drug
4	Marcus Washington, AV Staff (by videoconference)	4 Development Considerations for the Treatment of
5		5 Neonatal Enterovirus Infection and Congenital CMV
6		6 Infection. Thank you, all for joining us. Next.
7		7 We had a very productive Day 1
8		8 yesterday. In the morning, we heard about the general
9		9 principles of pediatric and neonatal drug development,
10		10 as well as an epidemiologic, virologic, and clinical
11		11 overview of enterovirus infection in neonates.
12		12 Then in the afternoon, we had a robust
13		13 panel discussion regarding the many enterovirus drug
14		14 development challenges. Key knowledge gaps were
15		15 identified, and potential solutions to some of these
16		16 challenges were proposed.
17		17 We have another ambitious agenda for
18		18 today. This morning, we will have epidemiologic and
19		19 clinical overviews of congenital CMV infection, as
20		20 well as several presentations regarding congenital CMV
21		21 drug development.
22		22 These morning sessions will serve to

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<p>1 set the stage for congenital CMV drug development</p> <p>2 panel discussions in the afternoon. Next, please.</p> <p>3 Before I turn the mic over to our first</p> <p>4 speaker of the day, I would like to reiterate some</p> <p>5 important housekeeping items.</p> <p>6 As noted yesterday, this meeting is</p> <p>7 being recorded. Speaker slides, transcripts, and</p> <p>8 recordings will be available on the meeting's webpage</p> <p>9 in the coming weeks.</p> <p>10 Speaker and panelist affiliations and</p> <p>11 voluntary disclosures are already available on the</p> <p>12 meeting's webpage under meeting materials. Note that</p> <p>13 this is the same webpage that you visited to register</p> <p>14 for the meeting.</p> <p>15 For all members of the general</p> <p>16 audience, your microphone and video camera are</p> <p>17 automatically turned off.</p> <p>18 Should you have any questions or</p> <p>19 comments, please submit them using the Q&A feature at</p> <p>20 the bottom center of your Zoom screen. We may not be</p> <p>21 able to respond to all questions and comments.</p> <p>22 Lastly, if you're experiencing any</p>	<p>1 DR. LANZIERI: Thank you, so much.</p> <p>2 It's a pleasure to be here, and thanks for the</p> <p>3 opportunity to speak with you today.</p> <p>4 Just one correction. I'm just the lead</p> <p>5 for the CMV Program. Measles and Rubella and CMV Team</p> <p>6 are under the leadership of David Sugarman.</p> <p>7 And to start, I have no conflict of</p> <p>8 interest, and the findings and the conclusions</p> <p>9 presented here do not represent the official position</p> <p>10 of CDC. Next, please.</p> <p>11 So many of you know this slide, based</p> <p>12 on estimates from newborn screening studies.</p> <p>13 Congenital CMV infection occurs in an estimate 4.5 per</p> <p>14 1,000 live births in the U.S., which corresponds to</p> <p>15 about 16,000 infected newborns just in 2020.</p> <p>16 As shown in the left-hand side, about</p> <p>17 10 percent of infected babies are symptomatic at</p> <p>18 birth. And off-label use of antivirals have been</p> <p>19 recommended for this group in the U.S. for over a</p> <p>20 decade.</p> <p>21 Fifty to seventy percent of these</p> <p>22 babies will have neurological impairment. And most</p>
<p>1 technical difficulties, please contact one of our</p> <p>2 outstanding AV staff, Corey Farley or Marcus</p> <p>3 Washington. Next slide, please.</p> <p>4 And we will now begin Session 1.</p> <p>5 During -- during this session, our presenters will</p> <p>6 provide epidemiologic and clinical background</p> <p>7 information regarding congenital CMV infection. We</p> <p>8 will also have the opportunity to hear parent</p> <p>9 perspectives on congenital CMV infection.</p> <p>10 We are thrilled to have Doctors Tatiana</p> <p>11 Lanzieri, Mark Schleiss, Roberta DeBiasi, and Megan</p> <p>12 Pesch here with us for this session. Next slide,</p> <p>13 please.</p> <p>14 So without further ado, I'd like to</p> <p>15 introduce our first speaker, Dr. Tatiana Lanzieri, the</p> <p>16 CMV Program Lead of the Measles, Rubella, and CMV</p> <p>17 Epidemiology Team at the Centers for Disease Control</p> <p>18 and Prevention.</p> <p>19 Dr. Lanzieri's talk is entitled</p> <p>20 "Surveillance in Epidemiology of Congenital CMV in the</p> <p>21 United States."</p> <p>22 Thank you, Dr. Lanzieri.</p>	<p>1 infants, 90 percent, are asymptomatic at birth. Ten</p> <p>2 to fifteen percent of them will have isolated</p> <p>3 sensorineural hearing loss that is congenital or has a</p> <p>4 late onset.</p> <p>5 The use of antivirals outside research</p> <p>6 studies has not been recommended for this group. But</p> <p>7 it is evolving. The recommendations are evolving.</p> <p>8 Of all infants with CCMV, 75 to 80</p> <p>9 percent have no long-term health problems, and this</p> <p>10 generates a lot of debate around universal newborn</p> <p>11 screening for CCMV, including concerns for</p> <p>12 overtreatment. And next, please.</p> <p>13 In the U.S.'s studies, 5 to 10 percent</p> <p>14 of hearing loss in children ages 2 years or less are</p> <p>15 attributable to CCMV. Sensorineural hearing loss</p> <p>16 occurs in about 50 percent of infants who are</p> <p>17 symptomatic at birth and 10 to 15 percent of the</p> <p>18 asymptomatic ones, as I said before.</p> <p>19 Prior to newborn hearing screening,</p> <p>20 these babies that appear well in the newborn exam and</p> <p>21 go on to later develop hearing loss, they were</p> <p>22 considered asymptomatic. So I'll not talk about --</p>

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<p>1 too much about asymptomatic. I will treat them as 2 isolated hearing loss.</p> <p>3 Importantly, up to half of the cases of 4 CCMV-related sensorineural hearing loss in either 5 symptomatic or isolated hearing loss may not be 6 detected by newborn hearing screening. Next, please.</p> <p>7 A few additional points to highlight 8 for children with CCMV and isolated hearing loss: The 9 hearing loss is typically progressive, does require 10 close audiology monitoring for early intervention; 11 two, children with -- who initially have unilateral 12 hearing loss have a higher risk of developing 13 bilateral loss.</p> <p>14 As shown in the survival curve on the 15 right, a higher proportion of infants with unilateral 16 congenital loss in red developed hearing loss in the 17 contralateral ear, as compared with infants with 18 bilateral normal hearing at birth in blue.</p> <p>19 By age 2 years, three in five of the 20 children with CCMV and isolated hearing loss will have 21 profound hearing loss, unilateral or bilateral, and 22 may become candidates for cochlear implants. Next.</p>	<p>1 Regarding surveillance, CCMV is not a 2 nationally notifiable condition. The standardized 3 case definitions for CCMV infection and disease were 4 approved in 2023.</p> <p>5 And currently, at least 12 states have 6 initiated surveillance efforts to monitor trends in 7 disease prevalence, connect families to resources and 8 services, and track compliance to hearing targeted 9 screening.</p> <p>10 Case ascertainment methods and data 11 collection vary. For case ascertainment, some states 12 rely on administrative data or clinical reports. 13 Others will include laboratory reporting.</p> <p>14 Few states collect data on long-term 15 outcomes. Thus, incomplete case ascertainment and 16 limited data on long-term outcomes contributes to 17 limited information on disease burden. Next.</p> <p>18 At CDC, congenital CMV was recently 19 added to the SET-NET and MAT-LINK. These are 20 surveillance systems to identify the impact of 21 emerging health threats on pregnant people and their 22 infants.</p>
<p>1 So I'm going to give a brief little 2 update on the status of newborn screening and 3 surveillance for CCMV in the United States. Next.</p> <p>4 In 2013, Utah began hearing targeted 5 screening, which means infants who failed their 6 newborn hearing screening are referred for CMV 7 testing.</p> <p>8 Several states and hospital networks 9 have followed with this strategy. And currently, Utah 10 also performs expanded targeted early testing for CMV 11 among infants who present with certain clinical signs 12 that lead to suspicion of CMV, but were -- earlier 13 not -- not all of -- all of them were tested.</p> <p>14 In 2023, Minnesota was the first state 15 to implement universal screening for CCMV, and we will 16 hear more about that in the next presentation.</p> <p>17 And in addition, New York State is 18 conducting a pilot, and legislation has been approved 19 in Connecticut, pending implementation, and New 20 Jersey, pending inclusion in the recommended universal 21 screening panel, or RUSP, which CMV is not part of. 22 Next.</p>	<p>1 Five jurisdictions participate in the 2 CCMV SET-NET project in the first year, Minnesota, 3 Utah, New York, New Jersey, and Iowa, and two others, 4 Virginia, and Illinois, were added in the second year.</p> <p>5 More academic sites are participating 6 in the CCMV surveillance module in MAT-LINK. And the 7 initial goals of the surveillance projects are to 8 identify and evaluate methods for CCMV surveillance 9 and assess the visibility of longitudinal data 10 collection for infants with CCMV through the age of 3 11 years. Next.</p> <p>12 The ultimate goals of CCMV surveillance 13 are to inform clinical guidance, vaccination, and 14 newborn screening policy.</p> <p>15 We are on the building phase, and our 16 aim is to use surveillance data to monitor trends in 17 disease and identify groups at higher risk of CCMV, 18 characterize the clinical spectrum of disease, long- 19 term outcomes, and access to services, as well as 20 monitor trends in the use of antivirals, including 21 acuity and whether it is in line with recommendations, 22 as well as assess real-world effectiveness. Next.</p>

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<p>1 So while our surveillance data are in 2 the works, I want to share some findings from analysis 3 of administrative data. Next.</p> <p>4 This graph shows a slight increase over 5 time in the administrative prevalence of CCMV disease, 6 defined as the presence of CMV diagnostic codes within 7 four to five days of life.</p> <p>8 This scale is for 10,000, so infant 9 diagnoses are in order of magnitude of the estimated 10 prevalence, which as I said in the beginning was 4.5 11 per 1,000 live births. Next.</p> <p>12 Before I show data on antiviral use, 13 I'd like to revisit treatment recommendations for 14 various groups.</p> <p>15 Currently, as per AAP Red Book, 16 treatment is recommended for infants with moderately 17 to severely symptomatic CCMV disease who exhibit 18 multiple signs or -- or central nervous system 19 involvement.</p> <p>20 That consists of six months of oral 21 valganciclovir starting within the first month of 22 life. Intravenous ganciclovir may be used initially</p>	<p>1 delayed at a median 45 days, and median duration was 2 little -- a little less than 6 months.</p> <p>3 Half of infants with CCMV were not 4 prescribed antivirals. Neutropenia, in the last 5 column, was more common in treated infants. Next.</p> <p>6 We have seen the use of antiviral 7 therapy for infants with CCMV disease increased from 8 2009 to 2019, and the reason for the dip in the 2019 9 data for commercially insured infants is unclear.</p> <p>10 Next.</p> <p>11 When we look at the proportion treated 12 by CCMV disease category or disease severity category, 13 the degree of change is similar for infants with 14 either moderate to severely symptomatic CCMV disease 15 in line with recommendations and for infants with 16 isolated hearing loss, despite not being recommended 17 in the U.S. Next.</p> <p>18 In summary, today I gave a brief 19 overview of the dynamic landscape of U.S. newborn 20 screening, surveillance, and treatment recommendations 21 for CCMV. This momentum would likely increase 22 identification of infants with CCMV infection.</p>
<p>1 for those who are unable to take oral medication.</p> <p>2 For infants with isolated hearing loss, 3 there is no formal recommendation for antiviral 4 therapy in the U.S.</p> <p>5 Recommendations in Europe are evolving. 6 These infants have been considered by the European 7 Consensus Group to have CNS disease, central nervous 8 system disease, hence, a treatment recommendation, and 9 more recently, a six-week therapy has been 10 recommended, based on findings of the CONCERT study in 11 the Netherlands. However, limited data on long-term 12 efficacy exist. Next.</p> <p>13 We used electronic health records to 14 assess use of ganciclovir and valganciclovir among 15 infants with CCMV.</p> <p>16 And as you can see in the first row, 4 17 percent of infants with CCMV had ganciclovir 18 prescriptions starting at a median 13 days for a 19 median duration of 8 days.</p> <p>20 Thirty-three percent had 21 valganciclovir, and twelve percent had both antivirals 22 prescribed. The start of valganciclovir was a bit</p>	<p>1 And we have seen an increasing trend in 2 use of antivirals since 2010, mostly in line with 3 prior recommendations, but also for infants with 4 isolated hearing loss.</p> <p>5 This highlights the need for increasing 6 provider education and shared clinical decision 7 making, given limited data on long-term efficacy of 8 antivirals, as well as the need for assessing real- 9 world effectiveness of antivirals recommended off- 10 label and for developing new drugs.</p> <p>11 And I look forward for the discussions 12 today. Next. My acknowledgements to all who 13 contributed to this presentation, and thank you, so 14 much.</p> <p>15 DR. HODOWANEC: Thank you, very much, 16 Dr. Lanzieri, and my apologies for the oversight 17 regarding your affiliations.</p> <p>18 Next, I'd like to introduce Dr. Mark 19 Schleiss, an American Legion and Auxiliary Heart 20 Foundation Research Professor in the Department of 21 Pediatrics at the University of Minnesota Medical 22 School.</p>

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<p>1 Dr. Schleiss' presentation is entitled</p> <p>2 "CMV and the Maternal-Fetal Dyad: Whom to Screen, How</p> <p>3 to Screen, and When to Treat?" Thank you.</p> <p>4 DR. SCHLEISS: Thanks. Thanks, so</p> <p>5 much. I appreciate the opportunity to be here. I'll</p> <p>6 just -- up front, I'll just say I don't have answers</p> <p>7 to any of these questions in the title.</p> <p>8 But the next slide gets us started,</p> <p>9 anyway, and gives an overview of the problem with</p> <p>10 maternal screening, which is that we don't really have</p> <p>11 any recommendations in the United States from ACOG, a</p> <p>12 maternal antibody screening.</p> <p>13 This is really, largely a reflection of</p> <p>14 the fact that CMV's sort of prevalence is high among</p> <p>15 women of childbearing age and moreover that</p> <p>16 reinfections with transmission that can lead to</p> <p>17 symptomatic disease can occur in seropositive women.</p> <p>18 So this is a big challenge.</p> <p>19 Having said that, there are a lot of</p> <p>20 studies that have looked at combinations of IgG, IgM,</p> <p>21 and avidity index sero-screening. Dr. DeBiasi is</p> <p>22 going to talk about that a little bit.</p>	<p>1 about prenatal treatment with valganciclovir. And</p> <p>2 this study talks about or reviews a double-blind</p> <p>3 randomized control trial on 90 -- 90 pregnant patients</p> <p>4 with primary CMV infection acquired in the first</p> <p>5 trimester.</p> <p>6 And this was the paper in Lancet, now</p> <p>7 published a couple of years ago from the group in</p> <p>8 Israel, Shahar-Nissan, et al.</p> <p>9 They found that individuals who had</p> <p>10 primary -- serologic evidence of primary CMV infection</p> <p>11 did have some improvement in a positive amniocentesis.</p> <p>12 It was significantly less likely in the</p> <p>13 valacyclovir group, only 2 out of 19 amniocenteses in</p> <p>14 that study, compared to the placebo group, which was</p> <p>15 11 out of 48 -- excuse me, 11 out of 23 amniocenteses.</p> <p>16 And an important caveat there is that</p> <p>17 this was a study of a fetal infection, not a</p> <p>18 congenital CMV. The benefit was limited to those with</p> <p>19 first-trimester infections. The next slide goes into</p> <p>20 a more recent paper that looked not only at</p> <p>21 amniocenteses, but true congenital CMV infection.</p> <p>22 And so interestingly, in this more</p>
<p>1 And based on sero-screening and</p> <p>2 amniocentesis, there is some information about the use</p> <p>3 of high-dose valacyclovir that I'll come back to in a</p> <p>4 moment.</p> <p>5 In the next slide, I think we have the</p> <p>6 most recent guideline that I could find from the</p> <p>7 Society of Obstetrics and Gynecologists of Canada.</p> <p>8 And -- and it's interesting to reflect on this.</p> <p>9 Again, ACOG has not taken any formal position on this.</p> <p>10 Although, it's under discussion.</p> <p>11 But in provinces in Canada where IgG</p> <p>12 avidity testing is available, screening for primary</p> <p>13 CMV infection in the first trimester can be offered,</p> <p>14 especially in women who are at high risk, particularly</p> <p>15 women who have toddlers and young children.</p> <p>16 And so this has become a much discussed</p> <p>17 topic in many centers in the United States. And now</p> <p>18 that we have universal newborn screening in Ontario</p> <p>19 and Saskatchewan with other provinces on the way in</p> <p>20 Canada, it will be interesting to see how these</p> <p>21 recommendations evolve.</p> <p>22 The next slide summarizes the statement</p>	<p>1 recent study with the reference provided below, there</p> <p>2 was an effect of valganciclovir on the rate of</p> <p>3 congenital CMV diagnosis at the time of amniocentesis,</p> <p>4 but not at birth.</p> <p>5 And so this is an area that needs to be</p> <p>6 further studied and discussed. The next slide now</p> <p>7 shifts into what about newborn screening, and newborn</p> <p>8 screening for CMV -- congenital CMV, has largely</p> <p>9 fallen into these categories so called targeted</p> <p>10 screening or hearing targeted screening or universal</p> <p>11 screening.</p> <p>12 The next slide summarizes important</p> <p>13 data from Karen Fowler and others about asymptomatic</p> <p>14 congenital CMV and infants with hearing screen</p> <p>15 findings.</p> <p>16 And the next slide from the CHIME study</p> <p>17 shows that in Karen's study, there -- there was a</p> <p>18 significant proportion of kids who had passed their</p> <p>19 newborn hearing screen, but went on to have</p> <p>20 sensorineural hearing loss.</p> <p>21 And so I think this is the -- the</p> <p>22 central core of the issue with targeted screening is</p>

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<p>1 that we'll miss a substantial proportion of children 2 who go on to have sensorineural hearing loss, which as 3 we've heard is the -- the main driving force, I 4 believe, behind CMV screening to capture those 5 children and offer early identification and 6 intervention.</p> <p>7 The next slide summarizes the pros and 8 cons of whether or not universal congenital CMV 9 screening should be provided as a part of the 10 recommended uniform screening panel or RUSP.</p> <p>11 And as -- as many in the audience know, 12 there have been petitions to the committee on -- 13 advisory committee, on newborn screening, which have 14 not really been vetted yet because of concerns that 15 universal congenital CMV screening doesn't fit the 16 classic paradigm for universal screening tests.</p> <p>17 Those who are proponents of universal 18 screening point out the delay in hearing loss, the 19 progressive nature, the option of antiviral therapy.</p> <p>20 But as Dr. Lanzieri pointed out, most 21 infants are asymptomatic. And we do have, I think, a 22 real issue with overuse of antivirals, not to mention</p>	<p>1 treatment options might be. All areas of controversy. 2 The next slide then moves into the 3 issue of what do we use for universal congenital CMV 4 screening.</p> <p>5 And the landmark CHIMES studies of the 6 early 2000s demonstrated the dried-blood-spot PCR, 7 which obviously has a lot of appeal, because it's 8 collected on newborns, had a suboptimal sensitivity in 9 that perspective study, where saliva PCR had a very 10 high sensitivity.</p> <p>11 So most of the discussions in recent 12 years have been focused on saliva-based PCR.</p> <p>13 The next slide gets into some work that 14 I commenced seven or eight years ago now, chiefly in 15 collaboration with Sheila Dollard at the CDC and 16 colleagues at the Minnesota Department of Health.</p> <p>17 And here's a paper from Sheila's lab 18 that looked very carefully at extraction techniques 19 and methodologies.</p> <p>20 And with improvement in extraction 21 techniques, chiefly an improvement over the magnetic 22 bead-based DNA recovery scheme or profile that was</p>
<p>1 the generation of perhaps unnecessary parental anxiety 2 for screen-positive babies who actually have a good 3 prognosis for a normal outcome.</p> <p>4 The next slide gets into some of the 5 details on the advisory committee on inheritable 6 disorders in newborns and children. This was a 7 petition or a letter offered a couple of years ago 8 now.</p> <p>9 Megan Pesch, who is on this call and 10 will have a presentation later, was the driver behind 11 approaching the committee.</p> <p>12 And the Nomination and Prioritization 13 Workgroup concluded that there was insufficient 14 information to move the nomination forward for 15 universal congenital CMV screening, and these were the 16 five criteria that they outlined in their response 17 letter. It's available online.</p> <p>18 And they wanted to see more data from a 19 pilot study, a cleaner case definition, very 20 importantly, sensitivity of a screening test that 21 would be used, and not to mention the clinical utility 22 of those babies who would be identified and what the</p>	<p>Page 315</p> <p>1 used for the CHIMES study, we decided to take another 2 look at dried-blood-spot PCR.</p> <p>3 The rationale being that perhaps we 4 would see an improved sensitivity to -- in comparison 5 to the CHIMES study.</p> <p>6 The next slide shows what we pursued, 7 which was a study in six newborn nurseries in the 8 Greater Twin Cities area.</p> <p>9 In the upper left, you see a lonely red 10 arrow up there in St. Cloud, Minnesota, which is a 11 little bit more of a rural area, and we looked at 12 newborns in the -- chiefly in the normal newborn 13 nursery and obtained consent to swab their mouths for 14 dried-saliva PCR and to get some punches from the 15 health department to look for CMV DNA.</p> <p>16 The next slide shows some of the 17 laboratory approaches. I won't belabor the points. 18 I'll just say that my lab used a UL 83 based real-time 19 PCR detection assay that we had been developing for 20 quite a number of years. The CDC lab used an IE 1 21 primer set. And in my lab, we also did the saliva PCR 22 for comparison.</p> <p>Page 317</p>

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<p>1 The next slide shows the data results 2 that we took action on. Any baby that was screen- 3 positive, we used the Rawlinson, et al., criteria. 4 First of all, confirmed the diagnosis 5 with the urine CMV PCR, so we -- we didn't define a 6 child as having congenital CMV unless they had a 7 confirmatory urine sample. 8 And then we obtained an audiology 9 assessment, biochemical markers, ophthalmologic, and 10 had ultrasonography studies, and then defined one of 11 these four disease categories from the Rawlinson 12 criteria. 13 The next slide shows the actual symptom 14 categories, again, from Rawlinson, et al., and this is 15 an area that, as Tatiana alluded to, is also under 16 discussion in terms of which babies we end up treating 17 with antivirals. 18 Next slide shows the sensitivity and 19 specificity. This was an interim analysis. The final 20 analysis shows similar numbers. 21 In the University of Minnesota lab, in 22 the CDC lab, using different primer sets, sensitivity</p>	<p>1 The next slide has the sensitivity and 2 specificity for the final numbers from the study, and 3 the next slide has a summary of how these babies fell 4 out categorically. 5 And so 68 out of the 87 infants were 6 classified as asymptomatic by the Rawlinson criteria. 7 Although, two of those babies did go on to have late 8 onset sensorineural hearing loss, and we're still 9 following them, and I anticipate there may be 10 additional babies, because we know hearing loss can be 11 delayed. 12 In total, 11.5 percent have had some 13 degree of hearing loss in -- in the follow-up to date, 14 and 15 infants fell into a symptomatic category with 15 either mild symptoms or moderate to severe symptoms. 16 The next slide shows the clinical 17 sensitivity. So in addition to the analytic 18 sensitivity, we wanted to take a look at whether a 19 positive screening test identified a baby who went on 20 to have some sort of CMV-related problem. 21 And for this definition, I lumped 22 together both, babies who had the late onset hearing</p>
<p>1 of the dried-blood-spot PCR, analytic sensitivity in 2 the mid-70 percent range, we had some positives that 3 were negative in CDC and vice versa, so when we 4 combined the results, it got up in the -- in the 85 5 percent range for sensitivity. 6 The next slide shows the viral load 7 distributions in confirmed cases, and I just include 8 this slide to point out that we only have one false 9 positive in the dried-blood spot. 10 But a number of a false positives is 11 shown in red on the left side in saliva -- 12 interestingly, a lot of very low saliva viral loads in 13 babies who did have confirmed congenital CMV. 14 So it remains unclear whether a cut-off 15 in viral load and saliva PCR can be a defining factor 16 in deciding which babies need further workup and 17 confirmation. 18 The next slide shows the overview from 19 the study. In total, we ended up consenting just over 20 24,000 families and had 87 cases of confirmed 21 congenital CMV. So for an overall prevalence of 22 somewhere between three and four per thousand.</p>	<p>1 loss, as well as mild or moderate symptoms, and the 2 clinical sensitivity of the DBS was more robust than 3 the analytic sensitivity. 4 So an argument can be made the dried- 5 blood-spot testing will actually identify those babies 6 who go on to have problems. 7 We were judicious in the babies that we 8 offered treatment to, and most -- for the most part, 9 only symptomatic babies were treated with 10 valganciclovir. 11 I did have one family in a completely 12 asymptomatic category that did want treatment. And so 13 in a shared decision-making sort of model, we -- we 14 did treat that infant. But for the most part, we -- 15 we are very judicious in antivirals in this pilot 16 study. 17 The next slide shows the summary to 18 date the for where we stand with antivirals, and we've 19 heard a little bit about the recent study -- the 20 CONCERT study, from the Netherlands. 21 We had a plenary session at PAS just a 22 couple of days ago in which Mary Caserta presented the</p>

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<p>1 current Red Book recommendations for antiviral 2 therapy.</p> <p>3 And as many of you are aware, those are 4 being modified now, such that we can commence the 5 treatment of infants within 13 weeks of birth for 6 babies who have moderate to severe symptomatic 7 disease, including those who have CNS involvement.</p> <p>8 The recommendation is still for six 9 months of oral valganciclovir. But based on the 10 CONCERT study, the Red Book Committee, and the current 11 AAP statement, makes the statement that we can offer 12 six weeks of oral valganciclovir to those babies.</p> <p>13 And -- and so this will be an area of 14 considerable discussion hopefully during the workshop 15 this morning and as time goes by. It is, I think, 16 important that we can commence therapy out to 13 weeks 17 of age now.</p> <p>18 And it's been my impression that many 19 families feel tremendous pressure and stress that 20 they're racing the clock to complete this diagnostic 21 workup by 1 month of age, which often is very 22 difficult to get referrals to audiologists and</p>	<p>1 lot of get-togethers of families.</p> <p>2 And the next slide shows some really 3 landmark work done by another parent advocate, 4 Stephanie Steidl, and this is her child, Hank, who 5 actually was identified in our universal screening 6 pilot study and appeared to be asymptomatic at birth 7 and went on to have delayed onset CMV retinitis -- 8 kind of an usual case in its own right.</p> <p>9 But be that as it may, the next slide 10 shows the announcement just over a year ago now of 11 initiation of universal screening. Folks in my lab 12 group that were working on this, including Claudia 13 Fernandez and, you know, Mary Hernandez, and Mark 14 Blackstad. And here's Vivian all grown up now with 15 her brother and her mom.</p> <p>16 And so in the spring of 2023, we began 17 universal dried-blood-spot screening in Minnesota for 18 congenital CMV.</p> <p>19 The next slide shows where different 20 states are with this. We have legislation in 21 Connecticut, shown in green. As was alluded to, New 22 York is currently doing universal screening as well,</p>
<p>1 ophthalmologists and obtain neuro imaging studies.</p> <p>2 And so I think having a little buffer 3 of extra time is actually very important for these 4 families.</p> <p>5 Next slide summarizes where we got with 6 universal screening in Minnesota. This was actually 7 one of my patients, little Vivian Henrikson.</p> <p>8 I was talking with her mom in clinic in 9 2016, and we were certainly talking all the time about 10 the various state initiatives to codify a targeted 11 screening, and we thought, well, why don't we go down 12 to the state capital and see if we can capture some 13 attention.</p> <p>14 And it only took us six years to get a 15 bill through the Minnesota Legislature. But we found 16 some legislative partners who signed on.</p> <p>17 One thing that was extremely important 18 was negotiating the fiscal note with the legislation, 19 and the state budget surpluses that occurred in -- in 20 the immediate aftermath of COVID really were very 21 helpful. And we put together broad coalition. We got 22 a lot of public attention, a lot of media events, a</p>	<p>1 but under the aegis of a NIH-funded program.</p> <p>2 Although, they seem to show every sign of 3 incorporating that into clinical practice at the end 4 of that pilot study.</p> <p>5 And then two provinces in Canada, 6 Ontario and Saskatchewan, are doing universal 7 congenital CMV screening. Although, interestingly, 8 not under the aegis of the newborn screening programs, 9 but in Ontario under the aegis of EHDI, Early Hearing 10 Detection and Intervention.</p> <p>11 And that's, I think, an area for 12 discussion too; where does universal CMV screening 13 belong; does it belong in -- in newborn screening, or 14 does it belong in -- in EHDI? And that will be a 15 topic for future discussion as well.</p> <p>16 The next slide shows exciting 17 development by the American Academy of Otolaryngology 18 and Head and Neck Surgery, who endorsed universal 19 congenital CMV screening just a couple of months ago.</p> <p>20 We have not seen any endorsement from 21 other professional medical organizations in the United 22 States. Although, I think this too will be an area of</p>

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1 discussion in the years ago.	1 infection, review diagnostics both pre- and post-
2 Next slide then is where we stand with	2 natal, discuss features of symptomatic congenital CMV
3 future uncertainties. Apologies. Hold on.	3 infection in a little more detail, discuss prenatal
4 I think that's my cue that I'm just	4 and postnatal treatments, and then a brief overview --
5 about done. But these are some of the imaging	5 literally, one slide that just shows the many areas
6 findings that we struggle with: subependymal cysts,	6 that are being looked at to focus on screening,
7 leukostriate [sic] vasculopathy, does every baby need	7 prevention, diagnosis, and treatment.
8 an ophthalmologic evaluation, and as Tatiana alluded	8 Next slide. So I don't think we need
9 to, uncertainties about antiviral treatment.	9 to belabor this. But I just want to point out again,
10 My last slide, thankfully, is an	10 like all the other speakers have, the real crux of
11 acknowledgement slide. And I want to acknowledge	11 making these decisions about who to study, who to
12 Sheila Dollard and Tatiana Lanzieri at the CDC, Sandra	12 treat, is this conundrum that it's the -- the minority
13 Rosenthal at MDH, who has been a key partner in this,	13 of infants that are symptomatic at birth that have the
14 and then at the University of Minnesota, in	14 biggest sequelae and then a large number of children
15 particular, Erin Osterholm, who's been my partner in	15 who are asymptomatic, but still can have hearing loss
16 the CMV follow-up work, and then members of my lab	16 or developmental delays as they progress through their
17 group as shown here.	17 life.
18 Thank you. And I'm sorry about the	18 Next slide. And it's really these
19 dogs.	19 decisions that are difficult for families and doctors
20 DR. HODOWANEC: Thank you, very much,	20 to talk about together when making the decisions about
21 Dr. Schleiss for that wonderful presentation, and	21 treatment. Next.
22 thank you for sharing all the important work that	22 So for clinical manifestations at --
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1 you've been involved in, in Minnesota.	1 you know, at a big medical center, we get referrals
2 I am happy to now introduce Dr. Roberta	2 from a variety of ways. They may come through the
3 DeBiassi, chief of the Division of Pediatric	3 prenatal pediatrics program, through maternal fetal
4 Infectious Diseases and Robert H. Parrott Professor of	4 medicine physicians that have found abnormalities on
5 Pediatric Research at Children's National Hospital and	5 exam. They may come from the NICU in a baby who is
6 Research Institute.	6 transported. They may come from a nursery -- for a
7 Dr. DeBiasi will present "New Horizons	7 liveborn nursery.
8 in Clinical Diagnosis and Treatment of Congenital CMV	8 And I think when we think about
9 Infection." Thank you, Dr. DeBiasi.	9 designing these studies going forward, the way these
10 DR. DEBIASI: Thank you, so much, for	10 children will present clinically are also different.
11 the introduction and opportunity to participate in	11 So this is just on one slide, a summary
12 this meeting.	12 of many of the prenatal findings that can be
13 And I have to say, Dr. Kimberlin and	13 suggestive of congenital CMV infection and lead to
14 Dr. Abzug were who introduced me to the whole world of	14 referrals to our program.
15 congenital CMV back when I was fellow, and I have to	15 In the brain, there can be
16 point out that two of the organizers of this workshop	16 calcifications, ventriculomegaly, or microcephaly,
17 were fellows at Children's National long ago. So	17 pseudocysts in various areas, polymicrogyria,
18 it's -- it's amazing how things have progressed over	18 cerebellar hypoplasia.
19 time.	19 In the GI system, we often see
20 Next slide, please. So the objectives	20 hypoechoic fetal bowel, ascites,
21 are to briefly review the physical exam, lab,	21 hepatosplenomegaly, or calcifications within the
22 radiographic features of infection, congenital CMV	22 liver.

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<p>1 We can see fetal growth restriction, 2 pleural or pericardial effusion, amniotic fluid 3 abnormalities, hydrops, and then, importantly, 4 placental abnormalities, which, of course, is not 5 specific to CMV.</p> <p>6 When we see these findings and they're 7 referred to our congenital infection program, we offer 8 prenatal follow-up consisting of serial ultrasound 9 every two to four weeks to see how these abnormalities 10 progress.</p> <p>11 And it's of note that these 12 abnormalities can appear even up to three months after 13 a mother is initially referred due to a primary 14 infection. So you can't really clear the baby 15 prenatally, even for a significant period of time.</p> <p>16 Fetal MRI can diagnose CNS findings not 17 seen by ultrasound and at some centers is readily 18 available and certainly can be used on a research 19 basis, as we've done in some other countries.</p> <p>20 Next slide, please. So postnatal 21 clinical manifestations I think most people are 22 familiar with -- small for gestational age infants,</p>	<p>1 are infected are susceptible to actual cell death by 2 lysis or apoptosis.</p> <p>3 And the structural abnormalities really 4 depend on when in the gestational age of the fetus 5 that this infection of the neurons occurs.</p> <p>6 The pathogenic spectrum of -- or the 7 result of that infection, as I said, can be lytic 8 infection of the neuronal progenitor cells, or there 9 can be vasculitis, which results in loss of the 10 supporting vessels and blood flow to the developing 11 brain, or frank meningoencephalitis due to release of 12 inflammatory mediators.</p> <p>13 And the calcifications that we often 14 see -- and you'll see on the next couple of slides, 15 are from extravasation of blood from damaged 16 microvasculature.</p> <p>17 Next. So there are ocular 18 manifestations of CMV, which are considered CNS 19 disease. This is the typical chorioretinitis that you 20 can see here, and we can also see cataracts in 21 children. Next.</p> <p>22 And then these are some images of the</p>
<p>1 specifically those that are asymmetric, meaning the 2 head is small, whereas the rest of the body is not, 3 jaundice, which is usually a direct hyperbilirubinemia 4 and can be more prolonged than the physiologic 5 indirect hyperbilirubinemia of the newborn.</p> <p>6 The blueberry muffin rash, which is 7 shown here, which is raised, palpable, and actually 8 represents extra medullary hematopoiesis as a reaction 9 to the suppression of the cell line due to CMV or just 10 frank petechiae or purpura separate from the blueberry 11 muffin rash.</p> <p>12 And then shown on the right is 13 hepatosplenomegaly in an infant. Next. So CNS 14 infection, of course, is the most concerning and what 15 we are trying to prevent, if possible, or ameliorate 16 if present.</p> <p>17 And if CMV enters the CNS early in 18 development, this is when the most significant 19 structural damage to the brain can ensue.</p> <p>20 It's really unclear why fetal newborn 21 brains are more susceptible to CMV compared to the 22 adult brain. But obviously, the developing cells that</p>	<p>1 typical periventricular calcifications that are best 2 seen on ultrasound, less seen on MRI. But as I said, 3 MRI picks up some of the structural abnormalities 4 differently.</p> <p>5 So at our center, we like to use both.</p> <p>6 And we can talk about that in the discussion period 7 about the feasibility and some protocols to do that 8 without anesthesia under 2 months of age.</p> <p>9 Children can also present with just 10 lethargy, poor suck, or hypotonia as a manifestation 11 of CNS disease.</p> <p>12 We also can see periventricular cysts 13 of ependymal pseudocysts or white-matter 14 abnormalities, as well as atrophy or migrational 15 disorders, the most concerning of which is 16 polymicrogyria, in which the neurons do not migrate as 17 they are developing in a normal way and lead to 18 abnormal gyral patterns. Next slide.</p> <p>19 So this is a autopsy photo that -- that 20 demonstrates both microcephalic, as well as abnormal 21 gyral pattern where you don't see the gyri; it's 22 disorganized, and it's smooth.</p>

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<p>1 And this occurs in -- if the infection 2 occurs during the most critical period in the third to 3 eight week -- third to eighth week of gestation. 4 But CMV infection, even in the later 5 trimesters, although it will not lead to 6 polymicrogyria, can still lead to CNS problems, 7 including the problems within cephalitis and 8 microvasculature that we mentioned. Next. 9 And this is just another autopsy photo 10 to demonstrate. Around the large ventricles, you can 11 see the white periventricular calcifications, the 12 dilated ventricles, and the atrophic cortex, so very 13 thin cortex, very big ventricles. Next. 14 So hearing loss you've heard so much 15 about. I don't think we need to belabor this, because 16 I think prior speakers have given a lot of detail. 17 But the bottom line is that 18 pathogenesis is still poorly understood. There are 19 certainly direct effects. But there are also animal 20 models and "fetopsy" studies that suggest that 21 inflammation, as a result of the infection, may be 22 equally or more important in the development of the</p>	<p>1 someone who has a toddler at home, as was mentioned, 2 since children in daycare can be excreting CMV almost 3 all the time. If you go into a daycare center, 4 probably 75 percent of those children are -- are 5 excreting CMV. 6 If the CMV IgG and IgM are both 7 positive, this could represent either primary 8 infection or reactivated disease. 9 I don't have a pointer. But you can 10 see in the slide that there's a little gray bump at 11 the earlier time period on the X axis, and then a 12 little gray bump on the X axis further out. 13 And so if you have that IgM, one way to 14 distinguish if this is an early infection or 15 reactivated disease is to use the avidity index of the 16 IgG in which the avidity low suggests that this is a 17 primary infection, whereas if this is a now mature and 18 highly avid antibody for IgG, you're likely in that 19 second reactivated hump to explain the IgM. 20 But it also was pointed out, it's not 21 completely reassuring, even if you have a reactivated 22 disease, because that's a large number of women, and</p>
<p>1 progressive or late onset hearing loss. 2 And therefore, when we talk about 3 treatments that really currently target viral 4 replication, some centers have proposed targeting 5 post-inflammatory response or a combination thereof. 6 Next. 7 So diagnosis. Next. Prenatally, as 8 was alluded to, ideally, we would know the serostatus 9 of every woman prior to pregnancy. But that's just 10 not the case in the U.S. 11 I think all of us who have taken care 12 of these babies -- it's heartbreaking when a mom tells 13 us, "I didn't even know that CMV existed. Why didn't 14 someone even tell me this and give me the option of 15 knowing?" 16 So that's another area of discussion 17 for legislation and has been adopted in some states 18 about education, even if nothing else is done with 19 screening. 20 But if the CMV IgG and IgM on the 21 mother are both negative, that identifies a 22 seronegative mother, who is at risk, particularly</p>	<p>1 there still can be transmission to the infant. 2 If only the IgG is positive and the IgM 3 is negative, it's likely this is a prior infection. 4 But I must say, if it's obtained for the first time 5 from a pregnant mother who has symptoms, you still may 6 wish to do avidity. 7 And we have had women, just because of 8 timing issues, where they had lost their IgM. But it 9 really was a primary infection that was picked up by 10 the avidity testing. Next. 11 Amniotic fluid PCR is another area that 12 had been looked at most -- most, I guess, intensively 13 by Lazzarotto's group. And the idea here is that it's 14 very sensitive and specific, but it has to be done at 15 a certain time after symptom onset and gestational 16 age. 17 And the real research question is, are 18 there thresholds CMV viral is predictive of 19 symptomatic disease? There really have been 20 conflicting results on this. 21 Lazzarotto's data showed that over a 22 thousand copies was highly predictive that the fetus</p>

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<p>1 would be infected, over ten to the fifth was 2 predictive of symptomatic infection, and less than 500 3 cutoff was unlikely symptomatic. 4 But there's a gap in between, and -- 5 and other groups have not really found these clear 6 cutoffs, so it's unlikely how useful this will be. 7 Next. 8 Postnatal diagnosis has been talked 9 about in the prior speakers. We really have to 10 diagnose this in the first three weeks of life, 11 because the CMV is so prevalent out in the community, 12 and infants can be infected with CMV postnatally for 13 other reasons. 14 So really, to be secure with the 15 diagnosis in an asymptomatic child, you need to have 16 the testing in the first three weeks of life and, 17 therefore, getting the urine or saliva PCR or going to 18 the health department to get the neonatal blood spot 19 is really the ways that we -- we do this. 20 I mentioned that neonatal blood spot 21 has lower sensitivity. But as you've heard, there is 22 some exciting data that perhaps the sensitivity may be</p>	<p>1 photographs. 2 A CBC with differential to identify 3 anemia from a cytopenia, a liver panel to look at ALT 4 total and direct bilirubin, head ultrasound, and 5 depending on your center and accessibility, MRI 6 without anesthesia, ophthalmologic exam to evaluate 7 for retinitis. 8 And then a newborn hearing screen, 9 which should be repeated if failed, because there's 10 many kids who failed that initial screen, and then 11 when it's repeated in the nursery, it's not failed or 12 BAER consistently failed. Next. 13 So treatment, you've heard a lot about 14 this from our prior speakers, and we're going to talk 15 a lot more about it. Next. 16 This -- and I just want to go through 17 some of the things that come up very frequently that 18 we still get asked. 19 So hyperimmune CMV immunoglobulin, 20 there was a lot of interest in this in the earlier 21 part of the decade, mostly based on the study in 2005, 22 which was an uncontrolled clinical trial, which showed</p>
<p>1 higher. 2 I will say, depending on your state, it 3 may be easier or harder to get the blood spot. For 4 instance, in Virginia, they actually hand the blood 5 spot -- you know, one blood spot to the family when 6 they leave the nursery so that they have direct access 7 to their blood spot for whatever reason, whereas in 8 some other jurisdictions, it's nearly impossible to 9 get it, or they discard them in a very short period of 10 time. 11 Serology has less of a role postnatally 12 because of the maternal transfer of IgG to the infant 13 and the unreliability of IgM testing. 14 Next are postnatal evaluations to 15 identify symptomatic congenital CMV if you have the 16 infant in front of you and you're doing the consult 17 or -- or you're in your office and -- and wondering if 18 this child might have a symptomatic disease. 19 Very close attention to growth 20 parameters, particularly non-symmetric SGA, careful 21 physical exam of the liver, spleen, skin, and eyes, as 22 we mention for the reasons I showed you on the</p>	<p>Page 339</p> <p>1 protection of hyperimmune CMV immunoglobulin to the 2 mother versus symptomatic disease in both treatment 3 and preventative groups of women and showed 4 significantly increased specific IgG concentrations 5 and avidity. 6 In that uncontrolled study, there were 7 no adverse effects, and it really raised enthusiasm 8 for the controlled clinical trials to follow, and that 9 was published in New England Journal. 10 But in 2014, the randomized controlled 11 trial by Revello's group showed no difference in 12 incidents of congenital infection, clinical outcome of 13 congenital infection when it occurred, no differences 14 in virus-specific antibody, T-cell response, or viral 15 DNA, and adverse events that occurred in higher rate 16 in treated, which really dampened the enthusiasm. 17 Next slide. 18 There was an additional randomized 19 control trial in 2021, which was also published in New 20 England Journal, which actually was stopped due to 21 futility and the fact that there were adverse events 22 in the treatment group, including severe allergic</p> <p>Page 341</p>

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<p>1 reaction in the higher incidents of symptomatic side 2 effects.</p> <p>3 So the -- the state of the art now is 4 we do not use hyperimmune CMV globulin in pregnant 5 women who have CMV disease. But it does come up in 6 clinical practice. We get that question quite a bit.</p> <p>7 Next.</p> <p>8 For antiviral, there have actually now 9 been many groups that have looked at the efficacy of 10 valacyclovir at 8 grams per day, either in a divided 11 b.i.d. regimen or divided 2 grams four times a day 12 for tolerability.</p> <p>13 Most of these have shown no significant 14 safety issues, and most of these have shown some 15 effects. So for instance, Jaharmi's [ph] son showed a 16 reduction in the PCR positivity in treated compared to 17 non-treated women.</p> <p>18 Jackomar [ph] showed decreased 19 circulating fetal viral load, and Lorezbeil [ph] in 20 2016 again showed decreased fetal viral loads, as well 21 as a reduction in a higher percentage of asymptomatic 22 infants in those that were treated.</p>	<p>1 And after the CSG 102 trial, this was 2 the randomized trial for six weeks of intravenous 3 ganciclovir versus no treatment.</p> <p>4 And there really was an improvement 5 odds ratio of 5 for normal improved hearing in best 6 ear at baseline and at 6 months in the treatment 7 group, and the untreated group were more likely to 8 have hearing loss at 6 months -- 21 -- odds ratio of 9 21 and 1 year -- odds ratio of 10.</p> <p>10 A follow on neurodevelopmental study, 11 these same patients showed that the treated had a 12 fewer number of delays on their Denver Developmental 13 Inventory. But the drawbacks and uptake of using IV 14 ganciclovir were because of the need for prolonged 15 PICC line, neutropenia, and potential risks of 16 therapy.</p> <p>17 So there are also concerns about the 18 fact that viremia was suppressed on the -- the 19 ganciclovir, but a rebound in viral load after 20 stopping it, and the fact that we knew that the 21 hearing loss is progressive.</p> <p>22 So this really was laying the</p>
<p>1 And there actually has been a 2 subsequent meta-analysis of these three, as well as 3 some other studies, that concluded that this might be 4 considered.</p> <p>5 And I will say that we do offer this in 6 our congenital infection program to women in certain 7 instances, again, in a shared-decision model and with 8 a careful monitoring for side effects for the mother.</p> <p>9 Next.</p> <p>10 So "Postnatal Antiviral Treatment 11 Trials to Define Standard of Care," this is the 12 Collaborative Antiviral Study Group and now the more 13 recent iteration in 2019 of the Congenital and 14 Perinatal Infection Consortium, multiple centers 15 across the U.S. and -- and where I really learned 16 about this from, Dr. Kimberlin and Dr. Abzug -- next 17 slide, also included international sites.</p> <p>18 And to review the -- the pivotal 19 postnatal antiviral treatment studies -- this was 20 during my fellowship where -- when I started seeing 21 children, we couldn't do anything for them, other than 22 check for their hearing loss and do neuro exams.</p>	<p>1 ground work for the subsequent studies that suggested 2 more prolonged suppression could be beneficial -- next 3 slide, to both hearing and neurodevelopment.</p> <p>4 And this is the pivotal trial that now 5 has led to the standard of care of six months of oral 6 valganciclovir. There was, of course, an intermediary 7 study where the PK and dosing of valgan to achieve the 8 levels that were achieved in the IV ganciclovir trial 9 were figured out, and that is what was used in this 10 study.</p> <p>11 So this was six weeks versus six months 12 of therapy, 16 milligrams per kilo, twice a day, which 13 is what we use to this day. And at six months, there 14 were no differences. But at 1 and 2 years, hearing 15 was more likely to improve or stabilize in the six- 16 month treatment group.</p> <p>17 There were improvements on the Bayley 18 nerve developmental composite and receptive 19 communication scales, and less toxicity is seen 20 compared to the IV therapy trials, and this was 21 published in New England Journal. Next.</p> <p>22 So this is -- I'm not going to go into</p>

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<p>1 all the details, because I think the other speakers 2 have mentioned it. You know, there are many papers 3 that suggest there's a consensus. But unfortunately, 4 there's really no consensus still, because there's six 5 different groups with six different consensus.</p> <p>6 And, you know, to make it simple, if 7 you have severe disease, no one disagrees. And if you 8 have no disease, everyone agrees. But it's this 9 middle thing that we have a hard time deciding.</p>	<p>1 So the future -- this is my last couple 2 of slides. If you go to clinicaltrials.gov, there's 3 61 trials that are U.S. and international that have 4 focused on or are currently focusing on congenital 5 CMV. And I break these into those that target the 6 prenatal period and those that are postnatal.</p> <p>7 So for prenatal, the areas are 8 identification of fetal or prenatal biomarkers, 9 including maternal viral load, cytokines, genetics, 10 and using proteomics to do so.</p>
<p>10 And specifically, does sensorineural 11 hearing loss isolate account as symptomatic or not? 12 Even within a center, people will disagree on that and 13 have differences about should the treatment be offered 14 or not in the shared decision model or not.</p>	<p>11 There are also prenatal intervention 12 and treatment trials that talk about behavioral 13 modification, prevention with vaccine, the passive 14 immunity trials that we've already talked about, and 15 then the antiviral therapy, valacyclovir, already 16 mentioned, but also letermovir. Next slide.</p>
<p>15 And then most people agree, if there's 16 only a mild or transient jaundice, for instance, that 17 we would call that asymptomatic, but that if you had 18 that in conjunction with a variety of other mild 19 findings -- maybe three mild or moderate findings, 20 that you might offer treatment. Next slide.</p> <p>21 "Other Recommended Interventions."</p> <p>22 Once they come to us, we see them monthly to adjust</p>	<p>17 And then targeting the postnatal 18 period, there are studies that are focusing on 19 screening, both the targeted and all children 20 universal, and then a long list of things that are 21 being looked at for postnatal, including 22 monoclonal/cytotoxic T-cell lymphocyte therapy,</p>
<p>Page 347</p> <p>1 their dose for weight, because this is a time of rapid 2 weight gain, and to monitor toxicities while they're 3 on their six months of valgan.</p> <p>4 They get frequent audiology 5 evaluations, which again, different groups suggest 6 different things. But we use every six months for the 7 first five years of life, increased, of course, if 8 there's abnormalities found. But if still nothing at 9 five years, then annually until eight years.</p> <p>10 We refer to early intervention 11 programs. We have neurologic and neurodevelopmental 12 assessments every six months to a year using the ASQ 13 surveys.</p> <p>14 We have follow-up with ID annually, and 15 we act sort of as a home base for these families, 16 because there are multiple specialists, and we always 17 catch things that fall through the cracks and help 18 them get plugged back in.</p> <p>19 And then for children who do develop 20 hypertonicity or spasticity or other problems -- motor 21 deficits, physical therapy, and occupational therapy.</p> <p>22 Next.</p>	<p>Page 349</p> <p>1 expansion of valgan treatment to asymptomatic infants, 2 and then use of letermovir, which the Congenital 3 Perinatal Infection Consortium is currently doing as 4 an adjunctive therapy, and we're all very excited 5 about.</p> <p>6 And then expansion of treatment beyond 7 the neonatal period, which has been alluded to, 8 because families ask for this.</p> <p>9 The study that was just completed by 10 the Collaborative Antiviral Study Group did try this.</p> <p>11 We had a low end and did not see differences in 12 hearing outcome. But -- but as you've heard, other 13 studies have potentially shown a benefit, and that has 14 led to the change in the recommendations that perhaps 15 we can treat, at least out to 3 months of age. Next.</p> <p>16 So I just want to acknowledge all the 17 people that work in the Children's National Congenital 18 Infection Program, particularly Sarah Mulkey, who is 19 our fetal prenatal and neonatal neurologist, and Dr. 20 du Plessis, who leads that division.</p> <p>21 And I will end there.</p> <p>22 DR. HODOWANEC: Thank you, very much,</p>

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<p>1 Dr. DeBiassi.</p> <p>2 Next, I'd like to introduce Dr. Megan</p> <p>3 Pesch, clinical assistant professor, director of the</p> <p>4 Congenital CMV Follow-up Clinic in the Division of</p> <p>5 Developmental and Behavioral Pediatrics, Department of</p> <p>6 Pediatrics at the University of Michigan.</p> <p>7 We are thrilled to have Dr. Pesch join</p> <p>8 us today to provide us with her unique perspective as</p> <p>9 both a pediatrician and a congenital CMV parent.</p> <p>10 In her talk entitled "Living with</p> <p>11 Congenital CMV - Parent Perspective," Dr. Pesch will</p> <p>12 provide not only her own perspectives, but those of</p> <p>13 other congenital CMV parents, some of whom</p> <p>14 participated in our recent FDA-sponsored Congenital</p> <p>15 CMV Focused Patient Listening Session.</p> <p>16 Thank you, so much, for joining us</p> <p>17 today, Dr. Pesch.</p> <p>18 DR. PESCH: Thank you. It is an</p> <p>19 absolute honor to be here. I'm going to start out --</p> <p>20 actually, if you could advance to slide 4. There we</p> <p>21 go. Oh, back one. I guess it was 3. Thank you.</p> <p>22 So we're going to start out with an</p>	<p>1 perfect baby girl. She's the final member of your</p> <p>2 family, and everyone is absolutely overjoyed. You</p> <p>3 have two and a half months with her until your world</p> <p>4 comes crashing down when you find out that she has</p> <p>5 profound hearing loss.</p> <p>6 And your soul is absolutely crushed</p> <p>7 when you hear from the otolaryngologist that she has</p> <p>8 likely never even heard your own heartbeat.</p> <p>9 You have no idea what's going on. Even</p> <p>10 in utero for those last few weeks, everything seemed</p> <p>11 to be going perfectly well.</p> <p>12 You ask a bunch of your friends and</p> <p>13 doctors and around 4 months old, find out that this is</p> <p>14 congenital CMV, something that you had heard of maybe</p> <p>15 in the past, but not really. It's only a vague</p> <p>16 memory, and actually, just the C in that TORCH</p> <p>17 acronym.</p> <p>18 You -- imagine how you feel when you</p> <p>19 find out that if you had been in another part of the</p> <p>20 country or another part of the world, that you would</p> <p>21 have been counseled about how to avoid this virus</p> <p>22 during pregnancy; and had you been somewhere else, you</p>
<p>1 exercise. I want to have you all imagine and put</p> <p>2 yourselves in the shoes of our CMV families.</p> <p>3 So let's just take a minute and imagine</p> <p>4 that you are pregnant with your third baby. This</p> <p>5 might be more of a stretch for some of the people on</p> <p>6 the call than others. But just go with it.</p> <p>7 First, you have had two healthy babies</p> <p>8 already. They're at home. They're toddlers. You're</p> <p>9 exhausted. But otherwise, gosh, this pregnancy is</p> <p>10 going super well. You are doing absolutely everything</p> <p>11 your doctors tell you. You're taking your vitamins.</p> <p>12 You're going to all the appointments. You don't scoop</p> <p>13 the kitty litter, eat sushi or lunchmeat. Next slide,</p> <p>14 please.</p> <p>15 And when your baby is born, it's a</p> <p>16 girl -- your third girl. What a joy. She is perfect</p> <p>17 and absolutely kissable. There are a few dots on her</p> <p>18 face, and actually, she did fail her newborn hearing</p> <p>19 screening. But you're told it's likely fluids, and</p> <p>20 you have heard that before too, so you're not very</p> <p>21 worried. Next slide, please.</p> <p>22 You take her home and just love on this</p>	<p>1 possibly would have been tested for this virus during</p> <p>2 pregnancy; and had you lived in another part of the</p> <p>3 world, you may have been offered treatment for this</p> <p>4 virus during pregnancy; and if your baby had born just</p> <p>5 another state over, she would have been tested for</p> <p>6 this virus and offered treatment.</p> <p>7 Imagine that sense of betrayal, that</p> <p>8 sense of anger, and that sense of pure devastation</p> <p>9 when you realize all of these missed opportunities</p> <p>10 have happened to you and your family.</p> <p>11 Now, of course, this is my story. But</p> <p>12 this is a story of so many CMV families, and I think</p> <p>13 it's really critical that we hear their words today</p> <p>14 and try to put ourselves in the shoes to understand</p> <p>15 the huge impact that this virus has on the life of not</p> <p>16 just these babies, but those who love them. Next</p> <p>17 slide, please.</p> <p>18 So this -- this is my daughter. Her</p> <p>19 name -- is perfect. Our journey has been long. She</p> <p>20 was -- like I said, identified at 4 months, too late</p> <p>21 for antiviral therapies. Although, we did them</p> <p>22 anyways.</p>

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<p>1 She has bilateral sensorineural hearing loss, global developmental delay. Next slide, please.</p> <p>2 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.</p> <p>3 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.</p> <p>4 Next slide, please.</p> <p>5 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.</p> <p>6 Yeah, it turns out it was. Next slide.</p> <p>7 So that's a little bit more recent picture of Odessa [ph]. Like I said, she's autistic.</p> <p>8 She -- her world is completely different than mine.</p> <p>9 The apple really has fallen far from the tree.</p> <p>10 Although, it has been just an absolute joy and wonder</p>	<p>1 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.</p> <p>2 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.</p> <p>3 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.</p> <p>4 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.</p> <p>5 A lot of mothers, I see turn to other mothers online. So there are some very active social</p>
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<p>1 to get to experience her world.</p> <p>2 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 undeniable that it has really changed the course of her life and made things much more difficult for her.</p> <p>3 Next slide, please.</p> <p>4 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.</p> <p>5 There she is now. I mean, look at that face. Next slide. I can't help, but brag, you know.</p> <p>6 So let's talk about the perspectives and families with congenital CMV.</p> <p>7 So starting out in pregnancy, it's a fact that in this country, the vast majority of pregnant people are not counseled about CMV.</p>	<p>1 media groups, CMV Mommies and CMV Awareness in Pregnancy, are two of the Facebook groups that have thousands of members.</p> <p>2 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.</p> <p>3 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.</p> <p>4 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.</p> <p>5 "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."</p>

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<p>1 "My doctor said we can't do antivirals.</p> <p>2 I'm so scared about what's going to happen. Does</p> <p>3 anyone know any maternal fetal medicine specialists in</p> <p>4 "blank" City who will at least talk to me about</p> <p>5 antivirals?" Next slide.</p> <p>6 Then once the baby is born, there is</p> <p>7 often a diagnostic odyssey. If the baby has a</p> <p>8 diagnosis of CMV right away, the path is a little bit</p> <p>9 more straight forward. Although, the unknowns are</p> <p>10 plentiful.</p> <p>11 Many families are launched into this</p> <p>12 unexpected role as medical parents. And like I</p> <p>13 mentioned in my intro, there is a feeling of anger and</p> <p>14 being betrayed by the medical system. I think it is</p> <p>15 somewhat less if the baby is identified early on.</p> <p>16 But the feelings are still there,</p> <p>17 especially in terms of being directed towards the</p> <p>18 OB/GYN community, who parents, you know, perceive</p> <p>19 maybe didn't tell them, and, you know, could this have</p> <p>20 all been prevented -- or prevented. The what-ifs and</p> <p>21 could-haves and if-onlys are -- are abundant.</p> <p>22 And in infancy, a common thing that we</p>	<p>1 he probably had a fatal genetic condition. No one</p> <p>2 ever mentioned CMV." Next slide. Let's skip this</p> <p>3 one. Thank you. Next slide.</p> <p>4 There's also a lot of misinformation</p> <p>5 and discrimination out there. I think medical</p> <p>6 professionals, people in the community hear</p> <p>7 "infectious disease" and often think that CMV is -- is</p> <p>8 so contagious, like COVID or maybe even more.</p> <p>9 A lot of our families report that they</p> <p>10 are isolated, and this kind of adds to the trauma, I</p> <p>11 would say, of having this diagnosis in infancy.</p> <p>12 "The nurse literally ran out of our</p> <p>13 room when she found out our baby had CMV. She said</p> <p>14 she was expecting and couldn't take the risk of caring</p> <p>15 for our baby."</p> <p>16 "My infectious disease doctor told me</p> <p>17 that I should keep away from other people. She was</p> <p>18 wearing a full Tyvek suit when we were talking -- when</p> <p>19 we were -- when she was talking to me. I walked away</p> <p>20 from that appointment thinking I had a serious</p> <p>21 infectious disease and was at risk to her and other</p> <p>22 people."</p>
<p>1 see in social media and I see in my own practice, is</p> <p>2 that these precious moments are lost. You know, in</p> <p>3 hindsight, I had two and a half months before I knew</p> <p>4 my daughter was deaf.</p> <p>5 And, you know, I like to be a glass-</p> <p>6 half-full person when I can. I -- I had two</p> <p>7 precious -- two and a half precious months with her</p> <p>8 where I wasn't overwhelmed with this possibility of</p> <p>9 what CMV would be bringing into her life, and so for</p> <p>10 that, I'm -- I'm grateful, even though if I could do</p> <p>11 it all again, I certainly would have gotten her</p> <p>12 antivirals early. Next slide.</p> <p>13 Here's some quotes summarized from the</p> <p>14 FDA parent listening sessions. "The hardest thing is</p> <p>15 the lack of awareness and knowing that we were not</p> <p>16 given the knowledge to prevent this." "We were robbed</p> <p>17 of the ability to try to reduce CMV in pregnancy."</p> <p>18 Next slide.</p> <p>19 These are quotes paraphrased in social</p> <p>20 media. "By the time we found out about her CMV, it</p> <p>21 was too late for treatment." "We saw so many</p> <p>22 specialists. He got so many tests. We were told that</p>	<p>1 And this, of course, is -- is not true.</p> <p>2 CMV is transmitted through bodily fluids and not</p> <p>3 through casual contact or respiratory secretion. Next</p> <p>4 slide, please.</p> <p>5 "My son was kicked out of daycare, even</p> <p>6 before he started. The daycare director called the</p> <p>7 state health department, and they told her my baby was</p> <p>8 a risk to their staff. We don't tell anybody about</p> <p>9 his diagnosis anymore. We've been shunned too many</p> <p>10 times. I want to be open. But I do not want him or</p> <p>11 my older child excluded from other activities or</p> <p>12 social opportunity."</p> <p>13 And these are, quote, "summarized" from</p> <p>14 Instagram. New slide -- or next slide, please.</p> <p>15 So family life, these are partially</p> <p>16 taken from the family listening session, partly taken</p> <p>17 from a paper I wrote with Shelly Zappas and Amanda</p> <p>18 Devereaux, two medical CMV moms.</p> <p>19 So a lot of families feel, like, they</p> <p>20 have to just educate by existing. So many people</p> <p>21 haven't heard about congenital CMV, and having to</p> <p>22 explain over and over can be exhausting.</p>

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<p>1 "Every single part of our lives has 2 been affected. There are so many little things," is a 3 quote from one family.</p> <p>4 Often, families report leaving or 5 changing employment. There's stress on marriage. 6 Siblings often feel left out or become glass 7 children -- those children that get looked right 8 through when there are other kids with higher 9 priorities in the family. New -- next slide, please.</p> <p>10 In early childhood -- oh, I'm sorry.</p> <p>11 Next slide. I think these -- this is the older 12 version of my slides.</p> <p>13 So there's also the fear of the 14 unknown. "We live in anticipatory fear wondering what 15 else will happen; when will her hearing get worse; 16 what will -- will there be a point when we can't 17 control her seizures; what will life be like for her 18 when we're -- around? In some ways, I hope we outlive 19 her." Next slide.</p> <p>20 I wanted to end by sharing Dakota's 21 story. Dakota was a little girl who lost her life to 22 congenital CMV. She was just over 1 month old.</p>	<p>1 State. I'm willing to answer any questions you have. 2 I just want to continue being a parent to my daughter, 3 even though she's not here. I will help however I 4 can."</p> <p>5 And I think this sentiment is really -- 6 really rings true with so many CMV families. They are 7 devastated. But they want to help. They want to help 8 the next generation.</p> <p>9 And I think it's really important to 10 remember all those babies and pregnancies that were 11 lost to CMV. We spend so much time talking about the 12 hearing loss and the cerebral palsy, which certainly 13 are significant. However, the impact on lives is 14 much -- much greater than just those two things. Next 15 slide, please.</p> <p>16 So in summary, CMV is the worst. But 17 our kids are absolutely the best. We desperately need 18 more awareness, and families deserve answers and 19 treatment, and lives are lost to the lack of knowledge 20 and lack of treatment for congenital CMV. Next slide.</p> <p>21 Thank you.</p> <p>22 DR. HODOWANEK: Thank you, very much,</p>
<p>1 Her dad reached out to me on social 2 media, and we had some nice conversations, and he -- 3 he said I could use these direct quotes.</p> <p>4 "If we'd known about CMV earlier, we 5 could have made decisions as parents for her. But the 6 medical system made those decisions for us. We both 7 worked in healthcare, and we had a 2-year-old at home. 8 No one said anything.</p> <p>9 I'm still mad, because we were in a 10 large medical center in "blank" City. There's lots of 11 resources, and it seemed everyone just didn't want the 12 liability of treating a pregnant woman. We are both 13 pharmacists. We understand the risks better than 14 anyone." Next slide.</p> <p>15 "When she was born, we were told she 16 had a one-third chance of being deaf. No one told us 17 the whole truth about how bad CMV could be. And 18 Dakota had the worst-case scenario.</p> <p>19 I felt, like, the whole 34 days she was 20 in the NICU until she passed away, no one was ever 21 completely honest with us." Next slide.</p> <p>22 "We recently passed a law in Washington</p>	<p>1 Dr. Pesch. That was such a -- a powerful and moving 2 presentation. We really appreciate you taking the 3 time to share so openly your family stories and those 4 beautiful photos of your family. It -- it really 5 means a lot to us that -- that you were with us today 6 to -- to share that.</p> <p>7 In just a moment, we are going to open 8 up for clarifying questions and comments pertaining to 9 these sessions we've heard -- these presentations 10 we've heard in the first session.</p> <p>11 Before we do so, I do want to just 12 mention, if anyone is interested in hearing additional 13 quotes or -- or summaries from the patient listening 14 session that was conducted here at FDA, those are -- 15 there's a summary posted online.</p> <p>16 If you just Google "FDA patient 17 listening sessions," you can search for the one on 18 congenital CMV, and there's lots of, I think, really 19 enlightening discussion and content there.</p> <p>20 So with that, again, we will open it up 21 briefly for clarifying questions and comments. So 22 parent -- or panelists, please raise your hand in Zoom</p>

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<p>1 if you wish to ask a question, and members of the 2 public may enter questions into the Q&A box. 3 Okay. I think, Dr. Bo, you had a 4 question or comment? 5 DR. BO: Thank you, very much, for the 6 opportunity. We greatly appreciate Dr. Pesch's -- 7 such a moving presentation and Dr. Lanzieri's slides 8 and DeBiasi's very informative presentations. 9 I have a question in regards to -- 10 maybe a clarifying question, and potentially, maybe we 11 can extend it into the panel discussion later on if 12 it's -- time doesn't allow. 13 But one of the questions that we're 14 interested in asking is, how much of the clinical 15 manifestations related to CMV are originating from the 16 infection during gestation versus newborn? Thank you. 17 DR. HODOWANEC: Thank you for that 18 question. 19 Dr. DeBiasi, would you like to address 20 that? 21 DR. DEBIASI: Yeah. I -- I mean, it 22 really depends on which clinical manifestation. So</p>	<p>1 course, on low birth weight and extremely low birth 2 weight premature infants acquiring CMV in the NICU 3 setting, most commonly from breastmilk, and certainly, 4 it can cause short-term disease. 5 Whether it can cause long-term disease, 6 including hearing loss, is unknown. There are some 7 papers that suggest that extremely low birth weight 8 preemies may have some long-term risks. Certainly, 9 they can have short-term disease. 10 The whole issue of whether or not a 11 strategy should be adopted to prevent acquisition of 12 CMV in premature infants in a NICU setting is one 13 that's actively being researched in many centers. 14 But I -- you know, if the question is, 15 does intrapartum or postnatal acquisition of CMV 16 disease happen? Yes, but most commonly in preemies. 17 DR. HODOWANEC: Thank you, very much, 18 Dr. Schleiss. There's a couple of comments in the 19 public Q&A box that I'll just share with the larger 20 group. 21 The first commenter says, "That was a 22 very powerful -- that was very powerful, and really</p>
<p>1 for instance, like, if it's polymicrogyria, which 2 implies that it was an early in utero insult to the 3 neurons as they were trying to migrate and go where 4 they're supposed to, you know, that injury is 5 irreversible. So an antiviral treatment will not be 6 able to reverse polymicrogyria. 7 On the other hand, the hearing loss, 8 which is progressive, that might be a combination of 9 both viral effect, as well as an inflammatory response 10 that's happening in the vestibular area. 11 So it's really kind of variable, 12 depending on what the manifestation is. I hope that 13 answers your question. 14 DR. HODOWANEC: Thank you, very much, 15 Dr. DeBiasi. Oh, Dr. Schleiss, yes? 16 DR. SCHLEISSL: Oh, well, I -- I would 17 just add, I mean, if the question is, you know, does 18 postnatal acquisition of CMV or acquisition during 19 labor and delivery in the birth canal, which can 20 happen probably rarely, does that lead to sequelae in 21 babies? 22 I mean, there is a literature, of</p>	<p>1 appreciate sharing of all those quotes from parents. 2 It is so important to involve parents in decision 3 making and give that knowledge about this disease. 4 The quote that the medical system made 5 that decision for us was so powerful and something we 6 should all keep in mind." Yeah, thank you, very much, 7 for sharing that Alyssa [ph]. 8 And then we also have another comment 9 noting that this is sort of congenital rubella dþjþ 10 vu and commenting that they hope we have an effective 11 vaccine soon, which would be -- would be wonderful. 12 And then we have just a couple of 13 minutes left, and there's a question now in the Q&A 14 box. And the question is, "If the severity of 15 congenital disease varies by trimester, is there an 16 argument for first-trimester screening?" 17 And I don't know if Dr. DeBiasi or Dr. 18 Schleiss would like to tackle that one. 19 DR. DEBIASI: I'm going to leave that 20 one to Dr. Schleiss. 21 DR. SCHLEISSL: Well, yeah. I -- I was 22 hoping you would answer it, Roberta. I mean, I think</p>

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<p>1 the answer is, yes, there is a very powerful argument 2 to be made for first-trimester screening, and I would 3 hearken back to my slide from the Canada Obstetrics 4 and Gynecologic Association.</p> <p>5 I -- I would like -- I would hope that 6 ACOG would tackle this issue in some earnestness in 7 the -- in the coming months and years.</p> <p>8 You know, the -- the dilemma is that in 9 comparison to Europe, I think there are more pregnant 10 patients in the United States who may not be aware of 11 their pregnancies early enough in gestation to offer a 12 window of screening and, as we heard, possible 13 intervention with antivirals.</p> <p>14 But I think this whole issue of 15 maternal screening is -- is something we -- we need 16 to -- to really think about.</p> <p>17 And I would call attention to a 18 provocative, I think, very interesting paper from 19 Brigitte Faas' group that was just in eBioMedicine 20 that -- that exploited the use of noninvasive prenatal 21 genetic testing, which is often done to screen for 22 aneuploidies and -- and to look for -- for CMV and by</p>	<p>1 ultrasound being normal in babies that end up infected 2 and affected.</p> <p>3 DR. HODOWANEC: Thank you, Dr. 4 Schleiss.</p> <p>5 Dr. Pesch, I know you had started to 6 come off mute there before. Did you have any comments 7 that you would like to make?</p> <p>8 DR. PESCH: Oh, I just wanted to say 9 that I'll -- I'll pass that along to Dakota's dad, 10 the -- those nice comments.</p> <p>11 DR. HODOWANEC: Thank you, very much. 12 I'm sure that would be appreciated.</p> <p>13 And then this will be the -- the last 14 comment. I see that Dr. Bo has his hand raised again, 15 and then we will be going to break.</p> <p>16 Dr. Bo?</p> <p>17 DR. BO: Yes, thank you, very much. 18 Very quickly. Thanks to Dr. DeBiasi for -- for your 19 response. It makes complete sense what you are 20 saying.</p> <p>21 Somewhat related to what you had 22 presented with regards to monitoring -- CMV PCR</p>
<p>1 DNA -- PCR, and Dr. DeBiasi had a brief mention about 2 it in one of her slides as well.</p> <p>3 I think that's an important area for -- 4 for future -- future research as well.</p> <p>5 DR. HODOWANEC: Thank you, Dr. 6 Schleiss. And -- and we -- actually, we have a 7 follow-on question to that, which is, do all first- 8 trimester exposures show ultrasound findings?</p> <p>9 DR. DEBIASI: No. Yeah. The answer is 10 no.</p> <p>11 DR. HODOWANEC: Thank you, Dr. DeBiasi.</p> <p>12 DR. SCHLEISS: Yeah. Ultrasound is 13 imperfect. There's certainly plenty of babies with 14 severe CMV disease who have normal antenatal 15 ultrasounds.</p> <p>16 Now, when I'm evaluating these babies 17 clinically, I always ask particularly about the 20- 18 week ultrasound, which almost all pregnant patients 19 will get a 20-week ultrasound.</p> <p>20 The most common fetal ultrasonographic 21 abnormality in cases that are documented is echogenic 22 bowel, actually. But there are lots of examples of</p>	<p>1 monitoring, where there isn't really a standardized 2 well-accepted viral load in order to initiate 3 treatment.</p> <p>4 And I'm wondering, is one-time CMV 5 PCR -- is enough to catch the viral load kinetics and 6 the movement of the -- of the virus throughout the -- 7 the infection process?</p> <p>8 DR. DEBIASI: Yeah. I mean, your -- 9 your question is excellent. And Dr. Kimberlin is the 10 expert on this. I mean, this is, you know -- in 11 parallel, we didn't have time to talk about it. But 12 the studies that have been done to look for treatments 13 also have viral monitoring aspects of these.</p> <p>14 And there is a lot of variability in 15 both untreated, as well as treated infection, which 16 probably relates to both antiviral effective whatever 17 medications we might be using, but also the host 18 immune response, which is, you know, variable. So 19 it's very complicated.</p> <p>20 DR. BO: Agreed. Thanks, so much.</p> <p>21 DR. HODOWANEC: All right. Thank you, 22 very much, again, to all of our Session 1 presenters,</p>

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1 and thank you for all of these great questions and 2 comments. We will now go to a break, and we will 3 return for Session 2 at 10:40. Thank you.	1 to human CMV, and the gB glycoprotein antibody targets 2 are very similar between the two, so it's thought to 3 be a good model of the CMV species as well. Next 4 slide, please.
4 (Off the record.) 5 DR. HODOWANEC: All right. Welcome 6 back everyone. We will now begin Session 2, which 7 will focus on congenital CMV drug development 8 considerations.	5 So in the mid-80s is when CMV models 6 started to become developed in rhesus macaques. So 7 the first model did an intracerebral inoculation in 8 the fetal brain in the second trimester. And this 9 what the histology looked, like, of the brain. You 10 can see ventriculomegaly, and leptomeningitis was 11 present as well. Next slide, please.
9 During this session, we will hear from 10 Doctors Emma Mohr, Lindsay DeVries, Ryan Kau, Megan 11 Pesch, and Rachel Greenberg.	12 So the rhesus models have moved beyond 13 just looking for infection and -- and brain -- brain 14 abnormalities. I'm going to talk about today model -- 15 modeling congenital CMV infection in pregnancy, 16 studying postnatal CMV and transmission, and then 17 really the lack of studies of infant outcomes
12 It is now my pleasure to introduce Dr. 13 Emma Mohr, assistant professor in the Division of 14 Infectious Diseases, Department of Pediatrics at the 15 University of Wisconsin Madison. Dr. Mohr will be 16 discussing preclinical models of congenital CMV 17 infection.	18 following any of the prenatal infection models. Next 19 slide, please.
18 Thank you, Dr. Mohr.	20 All right. So one of the first studies
19 DR. MOHR: All right. Thank you, very 20 much. So I'm going to change the talk about humans 21 for a little bit and jump to a discussion of rhesus 22 macaques and the model of congenital CMV infection in	21 I'm going to talk about is a study that was done in 22 pregnant rhesus macaques, and this was looking at how
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1 them. All right. Next slide, please. 2 So rhesus macaques are a model of human 3 pregnancy and congenital CMV infection. They're 4 probably the model of pregnancy and fetal 5 neurodevelopments that most closely mimics humans of 6 all the animal models out there.	1 C4T-cells are important in protecting against severe 2 congenital disease. 3 So before this, there had just been a 4 few animals that were inoculated with CMV and looking 5 at infant -- or sorry, fetal outcomes, like brain 6 abnormalities. This was the first study to really 7 increase the sample size and look to see sort of more 8 broadly what happens to the fetuses.
7 So one of the reason that they are 8 considered a good model is that placental transmission 9 of species-specific CMV occurs in both of these 10 species. Fetal sequelae on the brain, including 11 ventriculomegaly, leptomeningitis happens in both 12 species as well.	9 So there are two groups in this study. 10 In Group 1, they depleted the T-cells right before 11 inoculation with C -- rhesus C and B during pregnancy. 12 And that's Group 1 in the top.
13 Rhesus macaques develop antibody 14 responses during pregnancy, just like humans do, and 15 T-cell responses are important in both rhesus and 16 human pregnancies.	13 You can see it both in red, the viral 14 loads of the plasma, and then in blue, the amniotic 15 fluid viral loads. Three of the four pregnant animals 16 that were T-cell depleted and had rhesus CMV 17 inoculation had fetal loss. The other animal had 18 documented virus in the amniotic fluid still.
17 CMV species are different between these 18 two, human and rhesus macaque, though. So when rhesus 19 are used for models, they have to use a rhesus- 20 specific CMV, which is endemic in colonies of rhesus 21 macaques all around the country.	19 In Group 2, those were immune competent 20 animals, and they were inoculated with rhesus CMV as 21 well. One of the infants that was liveborn had 22 pancytopenia. The liveborn infant in the T-cell
22 This rhesus is very similar in sequence	

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<p>1 depleted group had intrahepatic calcifications seen on 2 ultrasound and then neutropenia found after birth. 3 Next slide, please.</p> <p>4 So this model was expanded, because 5 they really wanted to see the phenotype and see if 6 they could rescue the phenotype with hyperimmune 7 globulin therapy.</p> <p>8 So the question was, does hyperimmune 9 globulin therapy improve pregnancy outcomes in the 10 severe phenotype of CD4T-cell depletion in this rhesus 11 macaque model.</p> <p>12 So they had three groups. The first 13 group did the T-cell depletion, followed by rhesus CMV 14 inoculation at the end of the first trimester. They 15 had two different hyperimmune globulin groups.</p> <p>16 The first was standard HIG, which they 17 applied right after the T-cell depletion and then an 18 hour before inoculating with rhesus CMV. And this HIG 19 was defined as a good binding against the rhesus CMV.</p> <p>20 The high potency HIG, in contrast, 21 these -- this preparation was found by good 22 neutralizing antibodies to epithelial cells, so</p>	<p>1 So here, inoculation of -- or 2 treatment -- pretreatment with HIG before infection 3 with rhesus CMV was protective. Next slide, please.</p> <p>4 So this was a very interesting model.</p> <p>5 But it's hard to say that this is a really good model 6 for human studies, because there are no T-cells 7 around. So how often does this mimic what happens -- 8 happens in human pregnancies?</p> <p>9 So another study was done looking at 10 vertical transmission in immunocompetent pregnant 11 macaques. And here, they did a similar setup where 12 they're inoculating right at the end of the first 13 trimester, doing lots of different maternal blood 14 draws, weekly amniocentesis to look for vertical 15 transmission to the fetal compartment, and then the 16 fetuses are harvested toward the end of pregnancy.</p> <p>17 So the graph there in B shows the 18 maternal plasma loads with the comparison between the 19 amniotic fluid positive and amniotic fluid negative 20 animals. Really, you can see that they overlap a lot, 21 and they have other graphs that show there were no 22 significant differences in the patterns of maternal</p>
<p>1 slightly different definition of what -- of what the 2 antibody was.</p> <p>3 And again, the timeline was T-cell 4 depletion and then a week or so later, administration 5 of the HIG product by inoculation with the rhesus CMV.</p> <p>6 Next slide, please.</p> <p>7 So again, they're looking at sort of 8 very black and white outcomes here, just seeing if 9 vertical transmission was seen by looking at CMV in 10 amniotic fluid.</p> <p>11 So the top, those are the controls.</p> <p>12 You see virus in the maternal plasma. You see virus 13 in the amniotic fluid in all of the animals, and then 14 variable levels of virus in the urine and saliva.</p> <p>15 And in the standard HIGs, these similar 16 things, vertical transmission or detection of virus in 17 the amniotic fluid was -- didn't occur in all the 18 animals. It occurred in two-thirds of the animals.</p> <p>19 And in the high potency HIG 20 administration, you see that vertical transmission of 21 virus to the fetal compartment where virus is detected 22 in the amniotic fluid was blocked.</p>	<p>1 viral loads between the amniotic fluid positive and 2 negative animals.</p> <p>3 Of the 12 animals that were infected in 4 this group, only 5 had transmission of virus to the 5 amniotic fluid that was detected. So it's not 100 6 percent vertical transmission in the model where CD4T- 7 cells are depleted. Next slide, please.</p> <p>8 All right. So now, I'm going to jump 9 to the other side of this. So there's been a lot of 10 the model development in the pregnancy side of this, 11 but not as much in the infancy side.</p> <p>12 And the infant side has really focused 13 on postnatal CMV acquisition, so it happens naturally, 14 and if you can establish a model of postnatal CMV 15 infection in infants. There have not been any studies 16 of antiviral treatment of prenatal CMV infection in 17 rhesus macaques. Next slide, please.</p> <p>18 So one of the earliest studies to look 19 at, sort of a postnatal CMV model in rhesus macaques 20 was to look at CMV oral inoculation in rhesus 21 macaques.</p> <p>22 So here, 4-week-old rhesus infants were</p>

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<p>1 inoculated orally, so just a syringe with -- with CMV, 2 and viral loads were measured in their urine, plasma, 3 and saliva for a year afterwards.</p> <p>4 For comparison, they also inoculated 5 five adult rhesus macaques orally as well and did the 6 same sort of studies. So the adults are in black, and 7 the infants are in -- in gray.</p> <p>8 So this graph shows the antibody 9 responses to CMV after this inoculation. So all of 10 the infants develop antibody responses within a short 11 period of time after inoculation, so showing that the 12 inoculation really worked to establish a persistent 13 CMV infection.</p> <p>14 The adults had variable responses. 15 Some required multiple inoculations to have a 16 successful infection. Next slide, please.</p> <p>17 So another big question that has faced 18 rhesus macaque researchers is -- is when CMV is 19 naturally acquired in colonies. So it is widespread. 20 But it's unclear when exactly in that sort of infancy, 21 early child -- early -- early years of life CMV is 22 acquired.</p>	<p>1 their breastmilk, saliva, and urine, and then infant 2 saliva over the first six months of life.</p> <p>3 So Mom's breastmilk had variable levels 4 of CMV found over the first six months of life of the 5 infants. Mom's saliva also had some CMV detected at 6 many different time points. The urine of the -- the 7 dam as well showed variable levels of CMV throughout 8 this time, and then infant saliva showed very sporadic 9 levels of CMV positivity.</p> <p>10 So this is interesting. So it didn't 11 go up and stay up. And I have a graph on the next 12 slide to show you that the researchers thought that 13 this was sort of sporadic shedding, not a persistent 14 infection that was established.</p> <p>15 So these are those same infants that 16 had the sporadic shedding of CMV in the first six 17 months of life. But you don't start seeing CMV- 18 specific IgG detected until after a year of age.</p> <p>19 So they didn't have any CMV IgG that 20 was their own and not transplacentally transferred 21 from Mom until very much sort of, you know, 15 months 22 or so of life, after they were weaned and after they</p>
<p>Page 383</p> <p>1 So this study looked at where CMV was 2 in 1-year-old macaques, 2-year-old macaques, and 3- 3 year-old macaques. And what they found was that 4 looking at 1-year-old macaques, there is not much 5 virus that's found in many of the macaques in the 6 urine, saliva, or the plasma.</p> <p>7 But by the time that they're 2 years 8 old, all of the rhesus have virus detected in the 9 urine and saliva and some -- some in the plasma. And 10 they see the same thing at 3 years old and adults as 11 well.</p> <p>12 So this suggests that sometime after 13 they turn a year old, after that weaning period, is 14 when they naturally acquire rhesus CMV infection. 15 Next slide, please.</p> <p>16 So another question that was addressed 17 by rhesus macaque study was trying to understand if 18 breastfeeding transmission of CMV occurs naturally in 19 the rhesus population.</p> <p>20 So what the study did was paired CMV- 21 positive moms with their infants that they -- that 22 they just gave birth to and measured viral loads in</p>	<p>Page 385</p> <p>1 were group-housed with other infants.</p> <p>2 So what they think here is that rhesus 3 macaques probably don't transmit by breastfeeding very 4 often. It's probably more interactions after that 5 breastfeeding stage where they acquire natural CMV 6 infection. Next -- next slide, please.</p> <p>7 All right. So this is my summary slide 8 here. So there are multiple congenital CMV models in 9 pregnant macaques. CMV infection is variable in 10 immunocompetent macaques.</p> <p>11 The other finding was that maternal T- 12 cells are really protective in helping against severe 13 congenital disease, which includes fetal demise and 14 preventive hyperimmune globulin blocks vertical 15 transmission.</p> <p>16 In infants, it's really postnatal 17 transmission that has been evaluated. What they found 18 is that infants are susceptible to CMV infection by 19 oral inoculation. CMV infection naturally occurs in 20 rhesus macaques by about 2 years of age, and then 21 breastfeeding CMV transmission probably doesn't occur 22 very commonly.</p>

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<p>1 So what are the sort of open areas in 2 the rhesus macaque model for studying congenital 3 infection?</p> <p>4 So one of the limitations is that 5 congenital infection is -- is variable in these 6 immunocompetent dams. So studying antiviral therapy 7 and offspring would be challenging when you don't have 8 every infant that's actually infected.</p> <p>9 And given the small sample size that 10 you need to have in these studies for cost and 11 limitation of animal numbers, that would be very 12 challenging.</p> <p>13 Fetal tissues for these studies have 14 really been prioritized for viral studies, rather than 15 any developmental studies.</p> <p>16 Again, probably because we're looking 17 for a very strong phenotype where you can see viral 18 positivity or not, rather than looking at infant 19 development studies over the first year of life.</p> <p>20 So while there are many challenges to 21 infant outcomes and treatment in the macaque model, I 22 think there's lots of room to help answer questions</p>	<p>1 the characteristics of hearing loss in general and in 2 congenital CMV, a little bit about hearing assessment 3 in the pediatric population, and then get into the 4 considerations for study design. Next slide.</p> <p>5 So we'll start with hearing loss in the 6 audiogram. This is something that -- next slide, most 7 of you probably know a little bit about, but maybe not 8 everybody, so I want to walk through it.</p> <p>9 So there are three main types of 10 hearing loss that audiologists typically treat.</p> <p>11 There's sensorineural hearing loss, which is the most 12 common hearing loss that you see in older adults. But 13 obviously, you see it in children as well.</p> <p>14 And that is hearing loss due to 15 pathology in the cochlea, the auditory nerve, or even 16 the central nervous system, and it is typically 17 permanent in nature. These are the people you often 18 see wearing hearing aids, cochlear implants.</p> <p>19 Conductive hearing loss is typically an 20 abnormal mechanical transmission of sound, getting 21 from the external or middle ear into the inner ear, so 22 things like an ear infection, some kind of blockage,</p>
<p>1 that maybe cannot be answered in human studies.</p> <p>2 Thank you.</p> <p>3 DR. HODOWANEC: Thank you, very much, 4 Dr. Mohr. Very informative.</p> <p>5 Next, I'd like to introduce Dr. Lindsay 6 DeVries, a scientific reviewer in the office of 7 product evaluation and quality in the Center for 8 Devices and Radiologic Health here at the FDA.</p> <p>9 Dr. DeVries talk is entitled 10 "Congenital CMV and Hearing Loss: Study Design 11 Considerations." Thank you, Dr. DeVries.</p> <p>12 DR. DEVRIES: Hello. Can you hear me 13 okay? If so, we can go to the next slide.</p> <p>14 DR. HODOWANEC: Yes, we hear you. 15 Thank you.</p> <p>16 DR. DEVRIES: Okay. Thanks. Sorry.</p> <p>17 Okay. So today, like, Aimee said, I'm 18 going to be talking about study design considerations. 19 I know that we've been touching on that a bit in this 20 workshop, so I'm going to try to bring it together 21 from an audiology perspective.</p> <p>22 So I'm going to talk just briefly about</p>	<p>1 often can be treated with medication or surgery. But 2 sometimes people do have hearing aids when they deal 3 with these chronic issues.</p> <p>4 And then a mixed hearing loss is just 5 what it sounds, like, a combination between a 6 conductive and a sensorineural hearing loss, which can 7 occur when people have chronic middle ear issues, and 8 as they age, they may get some more permanent hearing 9 loss, so we see that too. Go ahead to the next slide.</p> <p>10 So this is just one example of the 11 degrees or severity of hearing loss that we -- that we 12 treat, and this is how we categorize them. There are 13 different entities that have slightly different ways 14 of doing this, so this is just one example.</p> <p>15 But we typically categorize severity of 16 hearing loss as normal, sometimes slight, mild, 17 moderate, moderately severe, severe, and then to 18 profound. So it can kind of range the whole gamut of 19 the audiogram, which I'm going to go over here in just 20 a moment. So you can go to the next slide. Okay.</p> <p>21 So we'll break this down a little bit.</p> <p>22 We'll slow down for just a second, in case it's been a</p>

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<p>1 while since some of you have seen an audiogram, if 2 ever. So this is a little busy. But we'll break it 3 down.</p> <p>4 On the X axis at the top is frequency, 5 so from low to high frequency or more base sound to a 6 more treble sound. And on the Y axis is the decibels 7 or amplitude from a soft sound at the top of the graph 8 to a loud sound at the bottom of the graph, so as you 9 move down the graph, the hearing loss is more severe.</p>	<p>1 doing two different things, which is also something 2 that can happen in CMV. So just keep in mind it can 3 be a little bit all over the map. So let's go to the 4 next slide.</p> <p>5 Right. So I found this great recent 6 review on congenital -- hearing loss in congenital 7 CMV. So I -- I've kind of compiled some of the 8 takeaways from that, because I thought it was really 9 useful.</p>
<p>10 And so this is just one example that 11 shows what we call the "speech banana." So you see 12 that blue kind of banana-shaped circle in there with 13 the letters in there?</p>	<p>10 So just at a high level, congenital CMV 11 is responsible for hearing loss in 20 percent of 12 children that don't have any other risk factors for 13 hearing loss. So that's, you know, that's a pretty 14 high percentage.</p>
<p>14 This is an audiogram that people will 15 often use in pediatric clinics, because it emphasizes 16 the frequency range of specific sounds, more high- 17 frequency sounds, like, S and F, and lower frequency 18 sounds you can see, you know, like, Z and V, M, D, B. 19 And so this is a great counseling tool for parents.</p>	<p>15 One of the key takeaways, I think, from 16 this talk and others is that CMV-related hearing loss 17 tends to be highly variable. So it's often 18 sensorineural in nature or typically, and it can occur 19 in symptomatic or asymptomatic cases. But there are 20 some differences.</p>
<p>20 The blue marks here are indicative of 21 the left-ear hearing status. So you can see as you go 22 up in frequency, the -- the threshold increases,</p>	<p>21 So this type of hearing loss is often 22 more severe in symptomatic cases. And it's often both</p>
<p>1 meaning it gets worse. And then the right ear is in 2 red, which shows a much more severe hearing loss.</p> <p>3 These are just, like I said, examples. 4 But I'm going to be showing you a couple audiogram- 5 like figures later. So I just want to make sure we're 6 on the same page.</p> <p>7 But this is the audiologists' kind of 8 major tool. But we have a lot of other assessment 9 tools that we use, of course, otoscopy and looking in 10 the ear, tympanometry, and acoustic reflexes, looking 11 at function in the middle ear, and otoacoustic 12 emissions, which we'll talk a little bit more about 13 later, which are one way to measure some inner-ear 14 function.</p> <p>15 And I just want us to keep in mind, 16 especially in the context of CMV, that there are other 17 hearing loss characteristics. So you can have 18 unilateral hearing loss, hearing loss in one ear, or 19 in both ears. It can fluctuate. It can be 20 progressive.</p> <p>21 As you see on the graph to the left 22 here, it can be asymmetrical. So two ears can be</p>	<p>1 ears in symptomatic cases, whereas in asymptomatic 2 cases, it's more often seen in one ear.</p> <p>3 The poorer ear, if you have hearing 4 loss in both ears, often "worsens" earlier and faster 5 than the better-hearing ear. So even if you have 6 hearing loss in both ears, if one is worse than the 7 other, it tends to kind of degrade and get worse 8 faster.</p> <p>9 Irrespective of middle-ear conditions 10 that kids can get, like ear infections, the hearing 11 loss, the underlying potentially permanent hearing 12 loss, can fluctuate. So it can -- it can look better; 13 it can look worse. So it's -- it's a little tricky.</p> <p>14 It can also progress over the years.</p> <p>15 So the risk tends to reduce after the age of 5. But 16 that doesn't mean that your first audiogram will look, 17 like, your audiogram at age 4 or 5. So that's another 18 thing to consider.</p> <p>19 And it can be late onset. So I think 20 somebody had mentioned a late onset case earlier 21 today, early yesterday. But in 10 to 20 percent of 22 cases, at least in the literature, there is a late</p>

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<p>1 onset. So you can see looking through here, it's -- 2 it's very hard to pin down. You can go to the next 3 slide.</p> <p>4 Okay. So I don't want to read this at 5 you. But there was a study done. It's about ten 6 years old now. But it's a pretty good study that 7 looked at, kind of at a high level, the -- the rates 8 of asymptomatic and symptomatic children and it kind 9 of broke down their hearing loss characteristics.</p> <p>10 So this study looked at 68 children.</p> <p>11 You can see here 59 had symptomatic CMV and 9 -- 12 that's a typo; 59 had asymptomatic CMV, and 9 had 13 symptomatic. Sorry about that.</p> <p>14 So of the asymptomatic children, that 15 bigger cohort, there was hearing loss to be seen. So 16 16 had sensorineural hearing loss at their first visit 17 and 11 at their last visit in the study, basically 18 meaning that some of them had unstable thresholds, and 19 5 of them had fluctuated back up into a more normal 20 range, but unclear if it would fluctuate again.</p> <p>21 So this is just kind of a snapshot in 22 time. Of the -- of the symptomatic children, six had</p>	<p>1 But -- but a good chunk did. And I'm going to show 2 you. This is a lot. So I'm going to show you just a 3 couple examples on the next slide.</p> <p>4 So these aren't the best quality. But 5 I really -- I really did have trouble finding some 6 nice pictorial representations of audiograms in the 7 literature, for some reason.</p> <p>8 But what this is showing here is not 9 exactly an audiogram. On the X axis is time. So 10 we're going to be looking, you know, out -- in the 11 first case, up until they're -- what 12 years old and 12 the other case here 5 years old, so they followed 13 these -- some of these kids a long time.</p> <p>14 And on the Y axis, again, is decibels 15 from at the top, more normal hearing, to at the 16 bottom, more profound hearing loss. And the Xs in 17 both cases are the left ear -- yes, in this case they 18 are. It's a little different from how we would do the 19 audiogram.</p> <p>20 But the squares are the right ear -- or 21 I'm sorry, the other way around. Squares are the left 22 ear, and the Xs are the right ear. It throws me off,</p>
<p>1 sensorineural hearing loss at their first visit, and 2 five at -- five ears at their -- had sensorineural 3 hearing loss at their first visit and five at their 4 last visit.</p> <p>5 So fewer kids in this group, and only 6 one of them fluctuated back into the normal range. 7 But you can kind of see that most of the kids still 8 had hearing loss.</p> <p>9 And so the takeaway here is, of all of 10 these kids that had hearing loss at their last visit 11 in the study, ten of them had unstable hearing. And I 12 know this isn't adding up to 16. I keep forgetting 13 it's ears, not necessarily kids. Sometimes we break 14 it down between ears, which we'll talk about later.</p> <p>15 But ten had unstable hearing, and then 16 seven ears had instability exceeding 30 dB. So 30 dB 17 is a pretty substantial fluctuation. You're -- you're 18 moving those severity categories quite a bit.</p> <p>19 So 32 percent of the kids -- they did 20 them as meta-analysis, had sensorineural hearing loss 21 and -- or in the study, and 29 percent had unstable 22 thresholds. So not everybody had unstable thresholds.</p>	<p>1 because audiologists do it a little differently.</p> <p>2 But in any case, it doesn't matter 3 which ear is which. You can look at the -- at this at 4 first glance, and you can see that the ears differ, 5 you know, some hearing loss at some frequencies, not 6 at others, and over time, that will change in each 7 ear, but not necessarily in both ears.</p> <p>8 So it's a little all over the map. And 9 if you go to the next slide, it's the same thing. You 10 can see here these kids are a little bit younger. But 11 they tracked them out 30 months, 39 months, and you 12 can see that there's some stability there, and in some 13 cases, it got worse and stayed worse, and in some 14 cases, it kind of went all over the place.</p> <p>15 So just -- just a snapshot and an 16 example of how these can change over time. Go onto 17 the next slide.</p> <p>18 Okay. So we'll briefly go through 19 hearing assessment in the pediatric population. I 20 know some people touched on the ABR, the BAER. But on 21 the next slide, I want to kind of break these things 22 down in between a, quote/unquote, "objective hearing</p>

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<p>1 assessment and subjective."</p> <p>2 So more objective hearing assessments</p> <p>3 that we do in audiology, otoacoustic -- otoacoustic</p> <p>4 emissions is one particular test. It's often what you</p> <p>5 see in newborn hearing screenings. But you can</p> <p>6 actually do a more diagnostic test too where you can</p> <p>7 look at frequency-specific responses.</p> <p>8 And these are responses reported from</p> <p>9 the inner ear. They are typically represented of</p> <p>10 outer-hair cell functions, so you aren't necessarily</p> <p>11 capturing inner-hair cell functions. We don't need to</p> <p>12 get into that distinction for this talk.</p> <p>13 But it has its limitations in terms of</p> <p>14 interpretation. But it can indicate some degree of</p> <p>15 hearing loss, and that's why we use it when we screen.</p> <p>16 The gold standard, I think, for right</p> <p>17 now at least in the little ones -- in the neonates, is</p> <p>18 auditory brain stem response I'm sure most of you are</p> <p>19 familiar with. You put stickers on their forehead,</p> <p>20 behind their ears, and you can record the auditory</p> <p>21 nerve response to sound, and you can get an estimate</p> <p>22 of the child's hearing loss.</p>	<p>1 heard the sound.</p> <p>2 It's pretty neat, and it's pretty</p> <p>3 effective. But you often are doing it in the sound</p> <p>4 field and locate your specific information that way.</p> <p>5 So you would only have kind of a sense on how the</p> <p>6 better ear is doing, for the most part.</p> <p>7 There's also condition or play</p> <p>8 audiometry, which is kind of moving toward the adult</p> <p>9 audiometry. Between 2 and 5 years of age, they --</p> <p>10 they play a listening game, like putting a block in</p> <p>11 the bucket when they heard the sound or sometimes</p> <p>12 hitting a button that lights up.</p> <p>13 In some cases, especially as they get</p> <p>14 older, you can put in headphones and you can get some</p> <p>15 ear-specific information, and then finally, you can</p> <p>16 move them to -- congenital -- conventional audiometry</p> <p>17 in children 5 and older.</p> <p>18 I've been able to do it with some</p> <p>19 precocious 4-year-olds. But this is your classic</p> <p>20 hearing test where they raise their hand when they</p> <p>21 hear a sound, and they push a button, or you can get</p> <p>22 them to say something that -- that, you know, excites</p>
<p>1 These are also used as screening tools,</p> <p>2 especially after the initial screening has failed.</p> <p>3 But they can be diagnostic. You can look at frequency</p> <p>4 specific ABRs. They can get tricky, as we'll talk</p> <p>5 about, as kids get older, and they start to get</p> <p>6 squiggly.</p> <p>7 So if you go to the next slide,</p> <p>8 behavior assessment -- here, I guess I said,</p> <p>9 "subjective." But really, I like to think of that as</p> <p>10 behavioral hearing assessment in children.</p> <p>11 The next step after the ABR, if you're</p> <p>12 able to get some behavioral information, is visual</p> <p>13 reinforcement audiometry. This is often used for</p> <p>14 children from 6 months to 2 years of age.</p> <p>15 It can be difficult to get an ABR on a</p> <p>16 6-month-old, you know, unless they're just fast asleep</p> <p>17 and they don't move for a while.</p> <p>18 And in this case, often the child sits</p> <p>19 in the parent's lap, and they're kind of directed</p> <p>20 toward -- toward the midline. And then you have</p> <p>21 speakers on either side that present a sound, and the</p> <p>22 child turns their head, and that's how you know they</p>	<p>1 them, like, "I hear it," or something else.</p> <p>2 And you can get a conventional</p> <p>3 audiogram -- maybe not all the frequencies you want.</p> <p>4 But you can move in that direction. Okay. So next</p> <p>5 slide.</p> <p>6 So this is just from the review paper.</p> <p>7 I know other people here have -- have talked about</p> <p>8 some of their protocols at their centers that they use</p> <p>9 for assessing hearing loss in CMV. So this is by no</p> <p>10 means meant to represent all -- all approaches. But</p> <p>11 it's something to think about as we get into thinking</p> <p>12 about the study design.</p> <p>13 So at -- at the centers that they</p> <p>14 looked at, children were diagnosed with hearing loss</p> <p>15 after undergoing otomicroscopy, tympanometry, reflex</p> <p>16 threshold measurements, behavioral audiometry if</p> <p>17 they're able to get that, of course; they have to be a</p> <p>18 little older.</p> <p>19 Click-evoked ABRs and tone-burst evoked</p> <p>20 ABRs, those are just two different types of stimuli.</p> <p>21 We don't need to get into that here, but, you know,</p> <p>22 two types of ABRs.</p>

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<p>1 And they are doing these measurements 2 when possible every three months for that first year, 3 ever six months until they're 3, and then every year 4 after that up to 6 years of age, and then they likely 5 move into our classic audiometric care if they're 6 stable.</p> <p>7 So that's just something to kind of 8 think about, how often they are measuring this hearing 9 as you think about study development, because it's -- 10 it's quite a lot, and it changes over time, as does 11 their ability to perform these hearing tests. All 12 right. Next slide.</p> <p>13 Okay. Now we can get into what 14 everyone wants to hear. I know I moved through that 15 kind of fast. I hope that -- that most of that was 16 pretty basic for you all.</p> <p>17 So if you go to the next slide -- okay. 18 So I kind of have some general considerations here, 19 and then I know that people are interested in talking 20 about end points and how to time end points. That 21 came up yesterday in the panel discussion, and we 22 certainly talk about it again here.</p>	<p>1 So that could kind of lead into these 2 other two goals here. But maybe you want to show that 3 you can produce fluctuations in hearing loss with 4 these -- with a drug, let's say.</p> <p>5 So that's something to think about, 6 because it will inform your end points, and it might 7 even inform the timing of your end points and the kind 8 of data you're going to collect.</p> <p>9 So the next bit, I don't want to 10 persevere on, because other people have talked about 11 it in the ethics talk and in the rear-world evidence 12 discussions and elsewhere.</p> <p>13 But of course, a comparator group might 14 impact -- well, it definitely will impact how you 15 structure your end points or structure your study 16 design. You know, you may consider comparing 17 interventions to standard of care.</p> <p>18 And I'm just talking about hearing loss 19 here, keep in mind. So I'm -- I'm on this narrow 20 focus.</p> <p>21 I don't want to get too much into the 22 real-world evidence world. But, you know, there may</p>
<p>1 But when I was putting this together, I 2 was thinking about how I could -- you know, how 3 frustrating it is. But I -- I can't give you, you 4 know, one perfect answer. But I -- I think there are 5 some things you can think about as these things are 6 developed.</p> <p>7 And one of them, of course, it sounds 8 obvious, but I think is really important, is to 9 consider your treatment and study goals.</p> <p>10 So I heard a lot yesterday in the 11 discussions about preventing or stopping progression 12 of hearing loss, which, of course, is -- you know, 13 would be the goal; right?</p> <p>14 If they don't have to have severe 15 hearing loss in the first place, that's obviously the 16 ideal situation. But there are a lot of challenges 17 with that for many reasons.</p> <p>18 So, you know, depending on what you're 19 trying to do in your study, you may be looking at 20 preventing progression of hearing loss, maybe 21 improving existing hearing loss, or even trying to 22 just stabilize existing thresholds.</p>	<p>1 be centers that you're at, potentially, that have 2 available audiometric information for comparison in -- 3 in other populations or if there were -- other 4 children had diagnostic ABRs for whatever reason. 5 There may be some sort of comparator group.</p> <p>6 But these two things at a high level 7 will inform how you develop your end points, of 8 course. So on the next slide -- okay. So there's a 9 lot here, and we can get into it in the panel. But I 10 just want to kind of briefly go through it.</p> <p>11 So there's kind of three big areas here 12 that I thought about when thinking about developing 13 audiological end points -- of course, a big piece of 14 the demographics of your targeted population in any 15 study you're developing.</p> <p>16 So I know we've talked a lot about, you 17 know, early diagnosis and -- and kind of the -- the 18 critical period after birth for stabilizing children 19 that have a myriad of potential issues with CMV.</p> <p>20 But in terms of hearing loss, I'm 21 thinking about what age are they diagnosed with the 22 CMV, especially if, you know, it's asymptomatic and --</p>

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<p>1 and something emerges later. When were they diagnosed 2 with the hearing loss? That could vary depending on 3 any number of factors.</p> <p>4 So depending on what you're kind of 5 trying to do in your -- in your clinical trial or with 6 a drug or some kind of treatment, you know, there 7 might be differences among the population you're 8 looking at in -- in terms of when they were diagnosed.</p> <p>9 Age at hearing loss assessment will 10 impact the testing approach. So I touched on the 11 different testing approaches, the type of data you can 12 generate, you know, whether you are able to get an ABR 13 on a, you know -- I don't know, 1-year-old -- maybe 14 not.</p> <p>15 So you might be looking at something, 16 you know, less ear-specific information. You might be 17 looking at sedated ABRs, and maybe that's okay. But 18 it can complicate the kind of data you're generating 19 in terms of hearing status.</p> <p>20 And -- and also, keep in mind that some 21 children, especially as they get older, might be using 22 amplification, like hearing aids or even cochlear</p>	<p>1 maximal benefit with cochlear implantation. 2 And that approach can be taken I think 3 in other -- other types of studies where you have a 4 worse ear. You're looking at the maximal benefit from 5 treatment. You're kind of, quote/unquote, 6 "potentially getting that ear back" or "getting less 7 hearing loss."</p> <p>8 But I think other people brought this 9 up yesterday, and that's a good point that if -- if 10 you have someone with asymmetrical hearing loss, they 11 have a bad ear and a good ear. But they still have 12 hearing loss.</p> <p>13 If the worse ear doesn't get any 14 better, that doesn't mean that the better ear can't 15 benefit from some kind of treatment. So you may want 16 to focus on the better ear, depending on your study 17 goal or even both ears, you know, if your goal is 18 hearing loss prevention.</p> <p>19 It's kind of -- you know, it can be 20 difficult to prove a negative. But depending on what 21 the hearing loss looks, like, you don't want to throw 22 out the baby with the bathwater, I guess -- throw out</p>
<p>1 implants in one or both ears.</p> <p>2 So, you know, that -- that doesn't 3 preclude you potentially from doing a treatment or 4 measuring their hearing. But it could actually 5 introduce some opportunities for showing some -- some 6 functional improvement, hopefully, after some sort of 7 treatment, and we'll talk about that a little bit 8 more. But this is a heterogeneous group in a lot of 9 ways, or it can be.</p> <p>10 So test conditions for primary end 11 points, so of course, the test 12 conditions -- audiologic test conditions should 13 reflect your study goals. If you're looking at 14 preventing a hearing loss, you might structure your 15 end point differently than if you're looking at 16 stabilizing hearing loss, et cetera.</p> <p>17 Man, I wish I had an answer for you -- 18 for you on this one. We talked about it a lot in our 19 group. And there's just no perfect answer. But 20 traditionally, in some cochlear implant studies, 21 people would often focus on the worst -- 22 quote/unquote, "worst ear" to show, you know, a</p>	<p>1 one ear that did benefit, and just focus on, you know, 2 the poorer ear, if you -- if you think your treatment 3 might benefit both.</p> <p>4 So you really need to think about that 5 and let your study conditions reflect that, because I 6 don't think there's necessarily a wrong answer or 7 right answer here. But it needs to kind of tell the 8 story that your study is trying to tell.</p> <p>9 And as I mentioned, demonstrating 10 benefit through measuring functional outcomes is 11 something that we see a lot in CDRH and in other -- 12 other types of studies that -- that measure hearing 13 loss, frankly, in the drug arena as well.</p> <p>14 But if people -- if children are coming 15 to you, let's say, slightly older, they have hearing 16 aids fitted. They have hearing loss. You want to get 17 them fit as soon as possible.</p> <p>18 We do see people measure audiometric 19 improvement in what we call "aided conditions." So if 20 you want to see what their hearing sensitivity is 21 like, you would take off their hearing aids; you would 22 test them.</p>

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<p>1 But you can also show potentially that 2 maybe improved underlying hearing is also improving 3 some of their functional outcomes with their devices, 4 which is also a great thing. You don't have to have 5 normal hearing to have, you know, great functional 6 outcomes.</p> <p>7 We also look at measuring speech 8 discrimination in these conditions. So you give them 9 word lists. You show that they're, you know, able to 10 get more words right or even sentences as they get 11 older.</p> <p>12 And there are also, for younger 13 children, parental questionnaires. There's something 14 called ITmaze. You can work with parents to talk 15 through different aspects of their child's auditory 16 kind of awareness and sound awareness and interactions 17 like that as they get older even. And that will also 18 help inform some functionality.</p> <p>19 So I think that's something to consider 20 as well. The audiogram is one piece of the puzzle 21 that's showing that it actually is translating into 22 something meaningful for these children -- I think is</p>	<p>1 collecting ABR data. You may, you know, hit a point 2 in your study where you can get some behavioral data. 3 But it's not useful to you.</p> <p>4 You have to kind of think about that.</p> <p>5 How are they going to age in sort of the short-term of 6 your study and then long-term assessment, of course, 7 of hearing and even language post intervention.</p> <p>8 So you might want to assess stability 9 of hearing status over time. This can pose 10 difficulties, as discussed, due to the nature of the 11 CMV-related hearing loss. So it can fluctuate, 12 obviously, on its own.</p> <p>13 It can normalize in some cases and 14 never fluctuate again. It can get worse and never 15 fluctuate again. So it is tricky. But that is 16 something that -- that would be worthy of assessment 17 in the long-term and then even language development in 18 relation to hearing status.</p> <p>19 So getting back to those functional 20 outcomes, as children get older, they can be tested by 21 speech pathologists and shown that, you know, they 22 still have hearing loss; but their hearing has</p>
<p>1 also an approach you can take. All right. Next 2 slide. I think I'm almost done.</p> <p>3 Okay. So getting into time point 4 considerations, this is another thing I wish I could 5 answer for you. But I can't. It depends on your 6 study. But I kind of broke it down into two pieces 7 that I think are worth thinking about. And I think 8 people have touched on this before and how tricky it 9 is.</p> <p>10 So there's kind of this short-term 11 assessment of hearing status post some kind of 12 intervention. Obviously, the frequency of your 13 hearing evaluation and your time points are going to 14 vary depending on your treatment.</p> <p>15 Whatever your treatment is designed to 16 do, you may want to measure hearing every month, every 17 two months, every six months. It -- it just depends 18 on your approach.</p> <p>19 Obviously, children are going to be 20 younger for these evaluations, if you're enrolling 21 little babies in these studies. So that, of course, 22 impacts the data you can collect. You might be</p>	<p>1 improved; their functional outcomes have improved, and 2 their language development is on par with their normal 3 hearing peers, let's say. So that's another potential 4 approach long-term.</p> <p>5 So to move into, like, you know, FDA 6 speed, I kind of think of this as a pre- to post- 7 market balance when developing time points for 8 studies. Maybe propose a time point for your pre- 9 market application end point.</p> <p>10 You're coming into us with a study; you 11 want to get a drug approved up to a certain age, and 12 then maybe there's a continued follow-up in the post- 13 approval study space.</p> <p>14 And of course, these -- whether this 15 approach is viable is going to depend on your study 16 design, the proposed indications for use, your 17 intended population, marketing claims, those things.</p> <p>18 But it could be one way to sort of 19 capture these two time points without having to delay 20 innovation on -- on the drug development side too 21 much. All right. Next slide.</p> <p>22 I'm going to fly past this one. I</p>

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<p>1 don't know if I needed it. But I was kind of thinking 2 about developing a road map when you look at -- at 3 these studies, clearly defining your treatment and 4 your groups, carefully considering your intended 5 treatment population and the kind of data you can 6 generate when developing your end points, considering 7 short- and long-term assessment, looking at longer 8 term stability of the hearing status.</p> <p>9 And then depending on your study, 10 design and intervention, you may be able to consider a 11 pre- to post-market balance and how you're developing 12 your study and proposing your end points.</p> <p>13 And then my last slide here. So as 14 I've been reiterating, hearing loss in children with 15 congenital CMV is very often a moving target.</p> <p>16 This hearing assessment in children 17 changes with age, which can change the type of 18 obtainable audiometric information, also a moving 19 target as you're study goes on.</p> <p>20 And these factors are going to impact 21 how you develop your end points. And you have to keep 22 that in mind as you're developing the study -- kind</p>	<p>1 helpful to discuss some of these questions early on 2 in -- in a development program.</p> <p>3 I will now introduce Dr. Ryan Kau. Dr. 4 Kau is a medical officer in the Division of Health 5 Technology in the ENT Device Team within the Office of 6 Health Technology 1, Office of Product Evaluation and 7 Quality in the Center for Devices and Radiologic 8 Health at FDA.</p> <p>9 Dr. Kau's presentation is entitled 10 "Alternative Routes of Drug Administration." So thank 11 you, Ryan. We're excited to hear about this novel 12 consideration.</p> <p>13 DR. KAU: Okay. Thanks -- thanks, 14 Aimee. So today, I'm going to talk about specifically 15 one alternative route, which is the transtympanic 16 injection, and I want to provide an overview.</p> <p>17 And it's potentially used as a valid 18 administration for hearing loss indications and 19 specifically to this talk, congenital CMV hearing 20 loss. Next slide, please.</p> <p>21 So I'm going to go over the history of 22 transtympanic injection, the procedure itself, the</p>
<p>1 of, you know, the moving target of both their age and 2 development and the hearing loss.</p> <p>3 And one recommendation -- I'm not in 4 CDRH -- but we have a similar process in CDRH, you 5 could use the pre-IND process to come in and discuss 6 your proposed -- proposed protocol with FDA, which can 7 help guide you further before you kind of dive into 8 the -- the IND study process. And, you know, I would 9 leave that to CDRH.</p> <p>10 But, you know, there's certainly 11 mechanisms for coming in and -- and kind of proposing 12 what you want to do. And, you know, FDA has the same 13 goal as you to help these kids with hearing loss so 14 would work with you on developing a protocol as well.</p> <p>15 And I think that is my last slide.</p> <p>16 DR. HODOWANEC: Well, thank you, so 17 much, Dr. DeVries. We really appreciate you sharing 18 your audiology perspective on these various 19 assessments and end-point considerations. Very -- 20 very helpful.</p> <p>21 And yes, in CDRH, we fully endorse the 22 use of the pre-IND program as well. It can be very</p>	<p>1 anatomy of the cochlea, potential complications, and 2 advantages of this route of administration, and 3 specific considerations for the targeted population of 4 congenital CMV hearing loss patients. Next slide, 5 please.</p> <p>6 So transtympanic -- transtympanic 7 injections have been used as far back as the 1950s, in 8 which aminoglycosides were used to treat vertigo.</p> <p>9 Currently, corticosteroids and aminoglycosides are two 10 commonly utilized drug classes administered 11 transtympanically for off-label uses.</p> <p>12 Corticosteroids are used for sudden 13 hearing loss, Meniere's disease, autoimmune inner ear 14 disease, and aminoglycosides are still being used 15 for -- for those, specifically with Meniere's disease.</p> <p>16 Next slide, please.</p> <p>17 So the procedure itself, typically, 18 it's -- this is done in the office. This is mainly 19 done in adults, for the most part, currently. And 20 it's usually done with otomicroscopy.</p> <p>21 Patients are placed in the supine 22 position, and then the physician has the option to</p>

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<p>1 anesthetize the tympanic membrane site of injection.</p> <p>2 Delivery of the drug is then made through the TM, and</p> <p>3 basically, this is done through the needle perforating</p> <p>4 the TM and then injecting it into the middle-ear</p> <p>5 space.</p> <p>6 There is an option of placing a second</p> <p>7 hole to relieve pressure when injecting. And there's</p> <p>8 also another option of whether we would want to put a</p> <p>9 tympanostomy tube prior to injection, especially in</p> <p>10 patients where we are going to be providing current</p> <p>11 treatments.</p> <p>12 So after this is done, the patient will</p> <p>13 remain in the supine position, and the ear that was</p> <p>14 treated will be turned away from the ground. And</p> <p>15 typically, this is the position they will hold for the</p> <p>16 next 10 to -- to 30 minutes.</p> <p>17 The patient is told to refrain from</p> <p>18 chewing or attempting to pop their ears or yawning,</p> <p>19 because we don't want the medication to drain from the</p> <p>20 Eustachian tube. Next slide, please.</p> <p>21 So this slide, you can see a needle</p> <p>22 going through the TM into the middle-ear space. And</p>	<p>1 endolymph fluid. Of note, the scala tympani is the</p> <p>2 space that is attached to the round window, and of</p> <p>3 also note is that there is a blood-labyrinthine</p> <p>4 barrier, which is a barrier between the vasculature</p> <p>5 and the inner ear fluids, and this has been noted to</p> <p>6 be an obstacle in delivery of system drugs to the</p> <p>7 inner ear.</p> <p>8 So this can be a problem when giving</p> <p>9 systemic drugs to affect hearing -- hearing loss for</p> <p>10 hearing loss indication.</p> <p>11 Also note, in the lower diagram, there</p> <p>12 is the inner and outer hair cells and the inner --</p> <p>13 inner hair cells and outer hair cells are potential</p> <p>14 products for drug products to treat hearing loss since</p> <p>15 damage to these sites is often thought to be the</p> <p>16 etiology of some hearing loss.</p> <p>17 So whether a transtympanic route of</p> <p>18 administration would be beneficial for an indication</p> <p>19 would depend on the exact path of physiology of the --</p> <p>20 of the hearing loss.</p> <p>21 And so if a injury to the hearing</p> <p>22 function is thought to be occurring at the level of</p>
<p>1 as you can see, the Eustachian tube is connected to</p> <p>2 the middle ear and, therefore, allows for a drainage</p> <p>3 path of the drug into the nasopharynx.</p> <p>4 The picture here is somewhat misleading</p> <p>5 in that we would use a -- typically, use an ear</p> <p>6 speculum and along with usually a spider -- a spinal</p> <p>7 needle, which is longer than what this seems, like,</p> <p>8 here.</p> <p>9 But you can see that it does show you</p> <p>10 where the round window is in the cochlea, as well as</p> <p>11 the ossicular chain and the Eustachian tube.</p> <p>12 And oftentimes, when we inject, we are</p> <p>13 aiming towards the round-window membrane, because that</p> <p>14 is where we would want the drug to enter into the</p> <p>15 cochlea. Next slide, please.</p> <p>16 So the cochlea has three main fluid</p> <p>17 chambers -- just some basic anatomy, the scala</p> <p>18 tympani, the scala vestibuli, and the scala media.</p> <p>19 The scala tympani and the scala of vestibuli contain</p> <p>20 perilymph fluid, and they communicate at the apex at</p> <p>21 the helicotrema.</p> <p>22 And the scala tympani contains the</p>	<p>1 the inner ear, the -- there's a potential for benefit</p> <p>2 with this route of administration. Next slide,</p> <p>3 please.</p> <p>4 So this is a list of potential</p> <p>5 complications. By far, the ear pain and ear fullness</p> <p>6 are the most common adverse events, along with</p> <p>7 dizziness and headache. And these are typically</p> <p>8 transient.</p> <p>9 Persistent TM perforation can occur</p> <p>10 with any type of procedure where you're perforating</p> <p>11 the TM, and therefore, frequent injections and</p> <p>12 extended durations of these injections can increase</p> <p>13 the risk of persistent TM perforations. Next slide,</p> <p>14 please.</p> <p>15 So some potential advantages -- so the</p> <p>16 advantages of transtympanic administration are</p> <p>17 basically consistent with advantage of any type of</p> <p>18 local drug delivery to a target location, and in this</p> <p>19 case, it's the inner ear.</p> <p>20 It can allow for a lower dose and a</p> <p>21 higher local concentration of the drug. And this has</p> <p>22 been seen specifically with use of corticosteroids.</p>

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<p>1 The other advantages listed here can 2 contribute to the ability to have lower dose and 3 higher concentration of the drug. The -- the -- this 4 transtympanic administration avoids systemic side 5 effects of the drug, as well as first-pass effect.</p> <p>6 And in addition, it bypasses the blood 7 labyrinthine barrier. And overall, it could decrease 8 the systemic side effects and would allow for longer 9 duration of administration if needed. Next slide, 10 please.</p> <p>11 So what kind of considerations should 12 we think about for this congenital CMV hearing loss 13 population? I think the -- the biggest one is going 14 to be tolerability, obviously.</p> <p>15 I think since the congenital CMV 16 hearing loss population would be quite young, it's 17 whether this patient population would be able to 18 tolerate this type of administration.</p> <p>19 For example, you know, we would 20 consider whether -- whether transtympanic injection 21 would require going to the operating room and 22 requiring anesthesia or if this could be done</p>	<p>1 An excipient, such as a poloxamer or 2 407, which has been studied for its real pectic 3 properties, is an example of this. And where the 4 liquid is -- where it's liquid at room temperature, 5 but then becomes more viscous at body temperature.</p> <p>6 Next slide, please.</p> <p>7 So in some sense, transtympanic 8 injection has many established advantages for drug 9 delivery to the cochlea. Whether this would be a 10 potential use for patients with congenital CMV would 11 be based on weighing the advantages and disadvantages 12 of this route of administration with specific 13 considerations to tolerability in this younger 14 targeted population. Thank you.</p> <p>15 DR. HODOWANEK: Thank you, very much, 16 Dr. Kau. Very interesting. Some -- some food for 17 thought for all of us.</p> <p>18 We will now welcome Dr. Megan Pesch 19 back to our virtual podium. Dr. Pesch will be 20 switching hats and will now discuss neurodevelopmental 21 outcomes in children with congenital CMV, a wide 22 spectrum.</p>
<p>1 inoperative procedure.</p> <p>2 I think if it would require recurrent 3 anesthesia, I think that would be not ideal and likely 4 would outweigh the benefits of the local 5 administration.</p> <p>6 The patients could tolerate an 7 inoperative procedure. The viability of transtympanic 8 administration in congenital CMV hearing loss would 9 then depend on dose frequency and dose duration 10 expected for the drug.</p> <p>11 If there will be frequent dosing, 12 perhaps it would be more tolerable to actually place a 13 tympanostomy tube in the -- in the TM. If it's less 14 frequent or of a short duration, perhaps patients 15 could tolerate the -- an infrequent office injection.</p> <p>16 And also, less frequent dosing may -- 17 to -- to have less frequent dosing, you may require 18 the ability to have a longer drug exposure in the 19 middle-ear space to the round window.</p> <p>20 This could be done by formulating a 21 drug that would stay in the middle-ear space better 22 than perhaps just a -- better than just a solution.</p>	<p>1 Welcome back, Dr. Pesch. Thank you.</p> <p>2 DR. PESCH: -- so much. All right.</p> <p>3 Let's get into it. Next slide, please. Next slide.</p> <p>4 All right. So today, we'll talk 5 briefly about why congenital CMV can cause these 6 developmental differences, who is at highest risk of 7 developing delays and disabilities, specific areas of 8 disability delay and differences, patterns we see in 9 kiddos with congenital CMV, as well as treatment, 10 management, and support.</p> <p>11 And this will be a very brief overview 12 of a giant topic. Next slide, please.</p> <p>13 So why do we care about congenital CMV? 14 I probably don't have to tell you, because you all 15 have been here all day. It's a leading nongenetic 16 cause of neonatal and childhood hearing loss, and 17 today, we're really going to focus on the risk of 18 other neurodevelopmental delays. Next slide.</p> <p>19 So as we heard earlier this morning, 20 the pathophysiology of congenital CMV in terms of 21 severity, the earlier the virus is transmitted to the 22 growing fetus, the greater risk of severity of the</p>

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<p>1 sequelae there is.</p> <p>2 And that runs kind of in opposite</p> <p>3 direction of transmission, which we know increases</p> <p>4 over the course of gestation, so higher risk of</p> <p>5 transmission, lower risk of severity of sequelae with</p> <p>6 later -- later transmission in the gestation. Next</p> <p>7 slide, please.</p> <p>8 So this is just a very brief overview.</p> <p>9 But I like to think of the mechanisms of fetal injury,</p> <p>10 because it really helps me then think about the</p> <p>11 sequelae and how those are caused.</p> <p>12 So there are three main mechanisms --</p> <p>13 and this is a simple way of looking at it, but three</p> <p>14 main mechanisms of injury to the fetus.</p> <p>15 One is that placental injury. CMV can</p> <p>16 get into the placenta, into the villi, into that fetal</p> <p>17 maternal interface, cause inflammation, vasculitis,</p> <p>18 and in turn, can decrease blood flow to the fetus,</p> <p>19 which can cause end organ damage or even just those</p> <p>20 smaller babies that we can see with congenital CMV.</p> <p>21 CMV also loves fetal CNS cells. And as</p> <p>22 someone mentioned earlier today, the reason for</p>	<p>1 areas that we see in terms of the mechanisms of fetal</p> <p>2 injury. Next slide, please.</p> <p>3 So it's no wonder that we see a lot of</p> <p>4 CNS related neurodevelopmental sequelae in these</p> <p>5 kiddos. The one exception, I would say, would be the</p> <p>6 ear, so the hearing loss and vestibular disorders. I</p> <p>7 guess it's arguable. They're, like, CNS adjacent;</p> <p>8 right?</p> <p>9 So depending how you look at it or</p> <p>10 where you draw that line. But thinking about that</p> <p>11 early invasion of the fetal brain, that inflammation,</p> <p>12 perhaps decreased maternal blood flow through that</p> <p>13 placenta, you -- we can see motor-planning disorders.</p> <p>14 CMV tends to really love the</p> <p>15 vasculature around the basal ganglia. So even we can</p> <p>16 see more severe motor-planning disorders, like</p> <p>17 cerebral palsy, but then also some less severe</p> <p>18 ones -- the softer signs that I'll talk about in just</p> <p>19 a little bit.</p> <p>20 We can see more profound intellectual</p> <p>21 disabilities, slight learning differences or</p> <p>22 disabilities, certainly epilepsy. We see the visual</p>
<p>1 that -- loving the fetal CNS versus and adult or even,</p> <p>2 like, postnatal CNS is -- is unknown. But getting</p> <p>3 into those fetal CNS cells, especially early in that</p> <p>4 first trimester, can have a giant impact, especially</p> <p>5 on early brain development.</p> <p>6 And then everything -- I like to think</p> <p>7 of development, you know, everything downstream from</p> <p>8 that. If those early foundational structures of the</p> <p>9 fetal brain are not formed correctly, then additional</p> <p>10 structures, you know, it kind of -- it's almost, like,</p> <p>11 a logarithmic effect.</p> <p>12 And then, of course, there's the</p> <p>13 maternal immune response. Some maternal immune</p> <p>14 response is good. But some -- or -- but a lot can be</p> <p>15 too much.</p> <p>16 And of course, that maternal immune</p> <p>17 system is kicking in, revving up, throwing out</p> <p>18 cytokines, throwing out antibodies. But that, in</p> <p>19 itself, while they're attacking the CMV within the</p> <p>20 fetal cells, can disrupt that fetal cell replication</p> <p>21 and even apoptosis.</p> <p>22 So those are kind of the three main</p>	<p>1 loss and impairment, which again is from the</p> <p>2 chorioretinitis, which was discussed earlier -- also</p> <p>3 see autism.</p> <p>4 I put a star there, because this a</p> <p>5 point of some controversy in the literature.</p> <p>6 Although, in my mind, it really isn't controversial.</p> <p>7 These kids are just coming out of the woodwork in</p> <p>8 terms of what we see clinically. Next slide, please.</p> <p>9 So I won't belabor this point. We've</p> <p>10 put these kids into two buckets for so long; right?</p> <p>11 But we all know it's such a complex disease process.</p> <p>12 The two buckets just really don't suffice.</p> <p>13 And, you know, classically, we thought</p> <p>14 that it was the kids that were born symptomatic --</p> <p>15 that 10 percent, that are the highest risk of</p> <p>16 sequelae, which is -- is still certainly true.</p> <p>17 But the kiddos that are asymptomatic,</p> <p>18 you know, aren't completely home free, so to speak.</p> <p>19 They are still at risk of sequelae. Next slide,</p> <p>20 please.</p> <p>21 And again, I'm a simple person, just --</p> <p>22 so think of this in kind of a simple way. Symptomatic</p>

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<p>1 babies are -- have signs at birth. Many do have 2 SNA -- or sorry, sensorineural hearing loss, and most 3 go on to have a typical development. And then it's 4 vice versa for the asymptomatic kiddos. 5 "Clinically inapparent" is another way 6 that we've discussed describing these kiddos. And I 7 think that's just a lovely way to say it. Although, 8 they may too have sensorineural hearing loss, and most 9 do go on to have typical development. 10 And I -- I kind of put these "typical" 11 and "atypical" in air quotes or quotes, which I -- I 12 tend to love and use a lot in my vernacular. 13 But I really think that we -- some of 14 these studies that are going on right now -- these 15 lovely longitudinal studies that are really robust 16 when following these kids longer will give us some 17 more definitive answers about the development. 18 But there are so many holes in the 19 literature that I'm hopeful that most kids with 20 asymptomatic CMV do have stone-cold typical 21 development. But I'm kind of -- I'm a little hesitant 22 to say that with full confidence, just from what I see</p>	<p>1 all of these things go into, you know, any child's 2 development and prognosis and what they have access 3 to. 4 So I think important to keep these in 5 mind as we think about these kiddos who, you know, are 6 born how they're born. And while we're doing so much 7 to try to prevent CMV, you know, kind of when these 8 kiddos are born, you get what you get. 9 So what can we do to optimize these 10 long-term outcomes? And I think even beyond the 11 antivirals, we need more answers for these families. 12 Because after six months, kind of then what? 13 And, you know, we don't have great 14 answers to that, at least that are backed by data. 15 Next slide, please. 16 I am just going to say that one of the 17 theories around CMV and hearing loss is that it seems 18 to be drawn to the microvasculature of the inner ear. 19 But that's just one of the hypotheses. Next slide. 20 I'm going to skip over this. We just 21 had a lovely presentation earlier about CMV and 22 hearing loss, so I think CMV and hearing loss, it's a</p>
<p>1 in my biased clinical experience. Next slide, please. 2 And then if you could just click 3 forward. I think there's -- there we go. So again, 4 the -- but in general, we see the severity of sequelae 5 increasing with the severity of disease. 6 And I just put some of the other names 7 here that we refer to, the clinically inapparent, 8 apparent, CMV disease, CMV infections, and genetic 9 asymptomatic. Next slide, please. Oh, there you are. 10 Thank you. 11 But this is something that the studies 12 haven't really looked at so far. And it just seems so 13 obvious to me as a developmentalist. But other 14 factors that are really -- that impact long-term 15 developmental outcomes for any kiddo; right? 16 Maternal education, there have been a 17 couple studies that have controls for that. But what 18 about access to therapies or access to healthcare. 19 Some studies do control certain gestational age, but 20 not nearly enough. 21 Singleton versus multiple pregnancies, 22 socioeconomic status, social determinants of health,</p>	<p>1 thing. 2 These are -- I was looking at this 3 slide this morning, and I think it's a touch 4 misleading. So if you could just pay attention to 5 what I'm saying, so I can explain this. 6 So when we think about these kiddos 7 with asymptomatic CMV and long-term outcome, so the 8 longer you follow these kids in cohorts, the more -- 9 the higher the percentage that develop hearing loss. 10 So a lot of the cohorts say, you know, 10, 15 percent 11 by, like, you know, 4 or 5 years. But that's only in 12 the four and five years. 13 The couple of studies that have 14 followed kids even longer, over decades, have shown 15 percentages kind of higher, like, 15 to 20 percent. 16 This is the stat that I think is a little misleading. 17 In some studies of asymptomatic 18 children -- so this is not allcomers, but in -- within 19 the cohort, 45 percent have had gaze and vestibular 20 dysfunction, and then 30 percent within these cohorts 21 have had balance difficulties. 22 So whether or not that can be</p>

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<p>1 generalized to allcomers, I don't think that's really 2 known yet. But to say that these are significant 3 things that can impact kiddos with congenital CMV, 4 even those that are clinically inapparent. Next 5 slide, please.</p> <p>6 So just briefly, I wanted to mention 7 that I think we're learning more and more how 8 important longitudinal follow-up is for these kiddos, 9 maybe even into the teen years; and that congenital 10 CMV is -- is an indication for unilateral cochlear 11 implantation sometimes for other conditions.</p> <p>12 Especially associated with unilateral 13 loss, it can be a little bit harder to insurance hands 14 to cover it.</p> <p>15 I also say that cochlear implant 16 outcomes really vary for kids with CMV. And the 17 literature supports that. It seems to really depend 18 on other sequelae, of course.</p> <p>19 And so it's -- it's really tough, 20 because you've got this little baby, perhaps with some 21 soft brain abnormalities -- definitely with hearing 22 loss.</p>	<p>1 along with kind of having that low tone, low muscle 2 strength, or slower to develop, as well as vestibular 3 dysfunction. Next slide, please.</p> <p>4 Feeding disorders are something that we 5 see pretty frequently, and it seems to be -- and this 6 is more anecdotal, because it really is understudied.</p> <p>7 If you're -- if you get on the CMV 8 Mommies Facebook site, it -- it blows up when you talk 9 about feeding disorders and difficulties.</p> <p>10 There's a lot of differences in how 11 these kids seem to process textures or tolerate 12 different textures. There's also the coordination of 13 chewing and swallowing.</p> <p>14 And of course, this make sense for a 15 child who may have cerebral palsy or something more, 16 like a diagnosis of muscle and brain communication 17 differences.</p> <p>18 But there has also been some theories 19 about chewing and swallowing difficulties, perhaps in 20 these kids being associated with hearing loss and the 21 kiddos with profound hearing loss, not using those 22 muscles quite in the same way and having somewhat of a</p>
<p>1 And I think often my colleagues in 2 otolaryngology, you know, just look at a kiddo with 3 sensorineural hearing loss and, of course, hope -- 4 hope for the best in terms of language outcomes.</p> <p>5 But I think with these kiddos with CMV, 6 there can be so many soft things that interfere with 7 language acquisition that really, from the get-go -- 8 and this is my personal belief, that they need multi- 9 modal communication, so sign language, as well as 10 access to oral spoken language for CI recipients, 11 because it doesn't always go kind of in that textbook 12 way. Next slide, please.</p> <p>13 So briefly, just on the motor delays 14 and disabilities, a lot of these kids are floppy. 15 They just have this really low tone and slow 16 attainment of those motor milestones. Most of them 17 get there, which is great, but not walking until 18 18 months, 24 months.</p> <p>19 And I'm not talking about the folks 20 with cerebral palsy, but even those asymptomatic kids 21 something we see clinically.</p> <p>22 And then the poor coordination goes</p>	<p>1 slower gain in those skills.</p> <p>2 Again, it's just a theory. For these 3 kids, we do swallow studies, feeding therapy, 4 occupational therapy. Next slide.</p> <p>5 Communication disorders certainly 6 associated with hearing loss, coordination of the 7 muscles of the mouth can be challenging for a lot of 8 kiddos. I also think there is some layers here with 9 autism and social communication differences.</p> <p>10 And it is exceptionally tricky when you 11 get these kiddos with autism and hearing loss and 12 trying to kind of decipher what -- what comes from 13 what, which again is why I'm a strong believer in 14 multi-modal communication for these kids as early as 15 possible.</p> <p>16 And then you peel back what they don't 17 need and what they don't, you know, gravitate towards 18 as they grow up and kind of declare it themselves.</p> <p>19 Next slide, please.</p> <p>20 So autism, we have a paper coming out, 21 Dr. Lanzieri and I and the -- the group from the CDC 22 coming out later this month, which support -- which</p>

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<p>1 shows a 2.6 times increased risk of congenital -- or 2 sorry, autism with kiddos with congenital CMV. 3 Several studies have found this, many 4 in -- in small cohorts and anecdotally. I think just 5 it makes sense, because from what we know about 6 autism, you know, the epigenetics of it and also just 7 really for anyone who is a pediatrician or who has 8 worked with young kiddos.</p> <p>9 Any disorder that causes perhaps a 10 malperfusion of the placenta or risk of brain injury, 11 we always see, you know, prior risk of autism, just in 12 general in those populations. So it makes sense why 13 CMV would be -- would increase the risk as well.</p> <p>14 I think in these kids it's tricky; 15 right? Because it takes a while for the autism to 16 kind of come forth. And so they may need different 17 approaches to therapies and communication as well.</p> <p>18 Early intervention is always critical 19 for any of these delays. I think all kids with 20 congenital CMV should be eligible for early 21 intervention monitoring.</p> <p>22 With autism in particular, knowing the</p>	<p>1 this is all compounded by any sort of communication or 2 movement difficulties or sensory seeking tendencies. 3 It can be really tricky to disentangle all of this. 4 Next slide, please.</p> <p>5 So really, I think this is what we 6 should be moving towards or -- or some version of 7 this.</p> <p>8 You know, we see these kiddos and how 9 they are born. They're born symptomatic or clinically 10 apparent or, you know, whatever you call it, and then 11 asymptomatic, how they look at birth, but then their 12 functionality, how they develop over time is 13 influenced by a myriad of things and not just their 14 status at birth.</p> <p>15 So I think kind of using this 16 spectrum -- you know, I'm a developmental 17 pediatrician, so I love the spectrum.</p> <p>18 And, you know, I think this is kind of 19 more where we should be moving and thinking of these 20 kids' functional status, over time moving from this, 21 like, binary simplified how they were born at birth 22 predicts their forever outcomes. Next slide.</p>
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<p>1 higher risk, and these kiddos need support and not -- 2 I would say, cures, because we're not looking 3 necessarily to cure autism, but to help these kiddos, 4 you know, have -- lower their challenges, work on 5 their strengths, increase their social communication 6 in ways that are comfortable and true to themselves.</p> <p>7 And I also think -- I just wanted to 8 mention, there's this fascinating overlap between 9 autistic and deaf communities. The deaf community 10 really one that had taken on this rejected -- this 11 disability identity thing. You know, "We are deaf -- 12 big D, Deaf. We're proud. We're not broken."</p> <p>13 And we're seeing that now within the 14 autism community as well with the neurodiversity 15 movement. Next slide, please.</p> <p>16 There's also a increase in behavioral 17 disorders and challenges. We see externalizing 18 behaviors that -- like, kind of the aggression, 19 outward oppositional internalizing behaviors or more 20 that anxiety, depression.</p> <p>21 A lot of impulsivity in these kiddos, 22 even the asymptomatic kiddos. And then, of course,</p>	<p>1 And I'll end there. Thank you.</p> <p>2 DR. HODOWANEC: Wonderful. Thank you, 3 so much, Dr. Pesch. I would now like to introduce our 4 last speaker for Session 2, Dr. Rachel Greenberg, 5 Associate Professor of Pediatrics in the Division of 6 Neonatology at Duke University School of Medicine and 7 the Duke Clinical Research Institute.</p> <p>8 Dr. Greenberg will discuss clinical 9 "CMV drug development: Where do we go from here?" 10 Experience of the Pediatrics Trials Network." Thank 11 you, so much, Dr. Greenberg.</p> <p>12 DR. GREENBERG: Thank you, so much. My 13 name is Rachel Greenburg, and I'm a clinical 14 researcher, and I'm chair of the steering committee 15 for the Pediatric Trials Network.</p> <p>16 And I'm also a pediatrician, and my 17 clinical work is as a neonatologist taking care of 18 infant -- virtual connectivity interruption -- and so 19 the NICHD and through the legislation provided by the 20 Best Pharmaceuticals for Children Act has sponsored 21 the PTN to improve dosing, safety information, and 22 labeling.</p>

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<p>1 And the focus of PTN's work is 2 primarily on off-patent therapeutics, so medications 3 that have been used for a long time and are no longer 4 on patent, and there's not -- there's not a lot of 5 interest in -- in studying them outside of the -- the 6 sponsoring through the NICHD and the PTN. The next 7 slide, please.</p> <p>8 So here's the typical schematic that 9 shows the big picture of the very long and complex 10 process of drug development, and, you know, we've -- 11 if you've been in the space in the past, you've 12 probably heard that new drugs can take 10 to 15 years 13 to come to market.</p> <p>14 And so the role of PTN is we're coming 15 in after all of this -- after a drug has come to 16 market. But often, the oldest drugs were not -- were 17 not studied in children, but where clinicians are 18 forced to use some medications, and so we have to use 19 them without all of the safety and efficacy data that 20 would -- and dosing information that would have been 21 beneficial to guide us.</p> <p>22 So PTN comes in after all this is done,</p>	<p>1 to the FDA for review and consideration for possible 2 changes to those drug labels. Next slide.</p> <p>3 So there -- there are a ton of folks 4 involved in doing the studies that may have made this 5 effort successful. And including sites and 6 participants enrolled from all across the country, 7 this just shows those dark purple areas are -- are 8 places where children -- participants have been 9 enrolled in PTN studies.</p> <p>10 The light purple areas are areas where 11 we're expanding into at this moment, and so really 12 have covered the country in terms of places that were 13 able to conduct studies to find this important 14 information. Next slide, please.</p> <p>15 And this is the latest infographic just 16 to show the accomplishments of the -- of the PTN in 17 terms of what we've been able to find out in this 18 space. So we've enrolled over 12,500 participants, 19 and you can see the little icon there representing the 20 therapeutic areas that we study.</p> <p>21 We're really agnostic to therapeutic 22 area, meaning, you know, we will study anything from,</p>
<p>1 works with the FDA to -- to have a plan to -- to 2 perform the studies -- often phase 1 or 3 pharmacokinetic studies, phase 2, or safety studies, 4 and working with the FDA to review these data and 5 hopefully make changes to that drug label to reflect 6 what is that new data for safety and efficacy and 7 dosing. Next slide, please.</p> <p>8 So this is a sort of outline of what 9 PTN's pathway to changing a drug label looks like. So 10 as I mentioned, the NIH collaborates with the FDA, and 11 they establish a list of priority molecules that are 12 being used without -- without effective data -- data 13 on safety or efficacy. And they sponsor pediatric 14 trials.</p> <p>15 And the Pediatric Trials Network does 16 these. And Pediatric Trials Network consists of a 17 clinical coordinating center at Duke and a data 18 coordinating center at EMIS, and we connect those 19 studies in areas that are identified on the priority 20 list, either the medications or the therapeutic areas 21 that are of priority.</p> <p>22 And then those study data are submitted</p>	<p>1 you know, menial intensive care to cardiology to 2 pulmonology to infectious disease to psychiatry, 3 anywhere there is a deficiency in data.</p> <p>4 And the studies that we've done have 5 led to this -- this infographic is out of date as of 6 just last week, it's now up to 21 changes to 7 medication labels that we've affected as a result of 8 this effort. Next slide.</p> <p>9 So these are the molecules for which we 10 have either done the studies to support the data and 11 submitted the data CASIA to change the label to add 12 pediatric information.</p> <p>13 And we're just missing here oxycodone, 14 which is the most recent one. That was our first 15 molecule for which we added information with -- in 16 collaboration with the -- with the FDA and the -- the 17 NDA holders to the -- to the label for oxycodone in 18 the lactation space.</p> <p>19 So prior to that, there was no -- 20 really, very little information in the drug label on 21 how the drug was passed into breast milk, and now that 22 information is there.</p>

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<p>1 The one -- the label change that 2 occurred prior to oxycodone was fluconazole. And 3 because it's in that infectious disease space as well, 4 I thought I'd give that example just to illustrate, 5 you know, what we -- what -- what motivates us to do 6 these types of studies and, you know, how that might 7 be applied in the CMV space. Next slide.</p> <p>8 So for -- in the fluconazole label 9 before the -- the PTN studies, the old label contained 10 almost no information related to how to use this drug 11 in infants, even though it was commonly used in the 12 clinical setting to treat Candida or yeast infections.</p> <p>13 If you could go back, please. So those 14 infections are -- thank you, they're often fatal in 15 infants, and they cause long-lasting health problems 16 for infants that survive.</p> <p>17 So the label change was a result of 18 four studies, multiple analyses that were supported by 19 PTN, and much -- and negotiation with the FDA in terms 20 of how to incorporate that information.</p> <p>21 And now the new label contains 22 information on pharmacokinetics and dosing</p>	<p>1 in this population.</p> <p>2 So as part of a way to try to deal with 3 the magnitude of this problem, we tried -- we wanted 4 to create -- we had this idea of creating a master 5 protocol for hospitalized infants that could be used 6 to study multiple diseases and medications under a 7 single study.</p> <p>8 And so then we were looking for 9 particular disease areas and focuses that would be 10 high yield in terms of where the need was. The next 11 slide.</p> <p>12 So in terms of disease processes and 13 therapeutics of interest in the infant population, CMV 14 was absolutely high on our list.</p> <p>15 So as the -- you've heard today, most 16 clinicians use ganciclovir or valganciclovir to treat 17 congenital CMV that is symptomatic, recognizing that 18 as we heard from the last speaker, there are many 19 categories of -- of symptomatic in many buckets.</p> <p>20 But we -- just for -- for simplicity's 21 sake at this point, ganciclovir and valganciclovir are 22 used to prevent those outcomes that we don't want to</p>
<p>1 suggestions, including the use of a loading dose, as 2 well as information on the use of fluconazole for both 3 treatment and for prophylaxis or prevention of Candida 4 infections in full-term and premature infants.</p> <p>5 And we also added information for 6 pediatric patients on ECMO. So that's newly included 7 in the label as well.</p> <p>8 So that's just an example of the type 9 of work that -- that we do. And, you know, that -- 10 that label -- that FDA label provides the guidance 11 that then trickles down to -- to guidelines and 12 everything that clinicians use to treat patients. The 13 next slide.</p> <p>14 So the PTN is -- is -- absolutely has 15 been interested in infants for quite some time. So 16 infants, particularly hospitalized infants, but also 17 infants in the outpatient setting are -- are 18 frequently prescribed medications off label.</p> <p>19 We did a study looking at the top 50 20 medications used in infants with extremely low birth 21 weight, so born at less than 1,000 grams, and only 20 22 of those top 50 or 40 percent were FDA labeled for use</p>	<p>1 happen, so hearing loss and neurodevelopmental 2 impairment. And the use of these drugs is based on 3 existing data and consensus guidelines. Next slide.</p> <p>4 But the priority list of molecules 5 developed under the Best Pharmaceuticals for Children 6 Act includes infections and neonates as an area of 7 therapeutic need where there is -- you know, there are 8 quite a number of infections, including CMV, for which 9 there is actually not a molecule available, not -- not 10 a medicine available, according to drug labels that 11 are -- that are approved to treat these infections.</p> <p>12 So ganciclovir and valganciclovir are 13 included within this area of infections as drugs for 14 which label updates are needed. And so, you know, at 15 this point, clinicians are using these medications 16 according to consensus guidelines and according to 17 standard of care, but without FDA guidance, because 18 that information is not in the drug label.</p> <p>19 And you can see this is a study we did 20 looking at a large healthcare database, looking at 21 infants hospitalized in NICUs all across the country, 22 and on -- on the right graph there, you can see on the</p>

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<p>1 Vioxx is the proportion of infants.</p> <p>2 These are infants with -- diagnosed</p> <p>3 with congenital CMV who are treated with either</p> <p>4 valganciclovir and ganciclovir during their</p> <p>5 hospitalization in the NICU. And this is a NICU</p> <p>6 population.</p> <p>7 And then on the X axis, you can see</p> <p>8 over time that treatment for congenital CMV has</p> <p>9 increased over time to the point -- in the most recent</p> <p>10 data that we had at the time, over 75 percent of</p> <p>11 infants with congenital CMV in the NICU are being</p> <p>12 treated with valganciclovir or ganciclovir.</p> <p>13 And we actually didn't have data on</p> <p>14 symptomatic -- of symptoms of CMV, so it's -- it's</p> <p>15 likely that many of the untreated infants were -- were</p> <p>16 asymptomatic in this population. Next slide.</p> <p>17 So what is the evidence base for</p> <p>18 treatment and why isn't this information in the -- the</p> <p>19 labels for these medications at this point?</p> <p>20 So we've -- we've heard previously</p> <p>21 today about some of these landmarks that even --</p> <p>22 thanks to Dr. Kimberlin and his colleagues for -- for</p>	<p>1 the study had -- had measurement of the primary</p> <p>2 outcome of the hearing loss at 6 months of age, and,</p> <p>3 you know, this is really common in study -- you know,</p> <p>4 long-term follow-up is extremely challenging,</p> <p>5 particularly in the infant population. And so this</p> <p>6 was one potential issue with that study.</p> <p>7 And then in the same study, the primary</p> <p>8 outcome was actually designated ahead of time, as is</p> <p>9 the usual process when creating a clinical trial. But</p> <p>10 that the study did not show the efficacy in the</p> <p>11 primary outcome, which was the hearing benefit at 6</p> <p>12 months.</p> <p>13 Even though hearing benefit was shown</p> <p>14 at 12 and 24 months, because it wasn't the primary</p> <p>15 outcome, specifically there was some, you know,</p> <p>16 reservation and thought that there needed to be even</p> <p>17 more evidence to be able to include information in the</p> <p>18 drug label. The next slide, please.</p> <p>19 So, you know, there's also always the</p> <p>20 thought of developing new molecules or new routes of</p> <p>21 administration as we've heard about earlier today for</p> <p>22 this problem.</p>
<p>1 doing these, you know, hugely important studies in</p> <p>2 this space and, you know, being persistent over time</p> <p>3 to try to establish what we can do for infants with</p> <p>4 congenital CMV.</p> <p>5 So the first -- the 2003 study compared</p> <p>6 six weeks of ganciclovir versus placebo and showed</p> <p>7 prevention of hearing deterioration at six months of</p> <p>8 age.</p> <p>9 And the second study compared 6 months</p> <p>10 versus 6 weeks of treatment and showing that longer</p> <p>11 treatment did not have significant benefit at 6</p> <p>12 months, but showed improved hearing outcomes at 12 and</p> <p>13 24 months, as well as improved neurodevelopmental</p> <p>14 scores. Next slide, please.</p> <p>15 So that seems, like, pretty compelling</p> <p>16 data, and those data are the basis for which</p> <p>17 clinicians are using ganciclovir and valganciclovir to</p> <p>18 treat infants with congenital CMV. But both of these</p> <p>19 studies had, you know, some issue that have led</p> <p>20 regulatory bodies to think that more data are needed.</p> <p>21 So for the first study, although it was</p> <p>22 pretty compelling data, only 42 percent of infants in</p>	<p>1 But also, what about ensuring the</p> <p>2 appropriate use of molecules already on the market?</p> <p>3 And could PTN help to perform a well-controlled trial</p> <p>4 to add to the body of information to help establish</p> <p>5 efficacy. Next slide.</p> <p>6 So the problem with considering another</p> <p>7 trial for symptomatic congenital CMV is that, you</p> <p>8 know, it's -- it's generally felt and assumed that</p> <p>9 there is going -- there is going to be a lack of</p> <p>10 equipoise.</p> <p>11 And what do I mean by that? So the</p> <p>12 equipoise is the assumption that there's not one</p> <p>13 better intervention present, so we don't know whether</p> <p>14 treatment is better than no treatment. And even</p> <p>15 though there's, you know, according to -- you know,</p> <p>16 because of the issues I showed before, there's not</p> <p>17 extremely definitive data.</p> <p>18 There's really compelling data to</p> <p>19 support treatment, and that's data that most</p> <p>20 clinicians are treating and most families want to be</p> <p>21 treated. So next slide.</p> <p>22 So your -- you know, the -- the belief</p>

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<p>1 of clinicians and the belief of families when faced 2 with this -- with this disease is such that 3 there -- there could never be a placebo controlled 4 trial for infants with symptomatic CMV -- congenital 5 CMV, moving forward, because no one would want to 6 enroll in that trial, and, you know, it wouldn't -- it 7 wouldn't be felt to be, you know, some -- there 8 wouldn't be equipoise. So next slide.</p> <p>9 And yet, we're stuck with the current 10 drug labeling information where you -- you know, if 11 you open up the package insert for ganciclovir or 12 valganciclovir and you look under the indications, you 13 see in ganciclovir, there's no pediatric indication -- 14 and next slide, for valganciclovir there is a 15 pediatric indication that it's for prevention of CMV 16 in kidney transplant patients, so nothing that 17 addresses congenital CMV at all, even though these 18 drugs are used widespread. Next slide.</p> <p>19 So where do we go from here? And 20 we're -- we're -- we -- it feels, like, we're stuck. 21 And so we -- I know this will be part of the 22 discussion in the panels this afternoon. But, you</p>	<p>1 discussion was that, yes, in term infants, it's really 2 ubiquitous and -- and not an issue. 3 But in pre-term infants, postnatally 4 acquired CMV causes a symptomatic stress just, like 5 illness, and observational studies suggest that it's 6 also associated with adverse long-term outcomes. 7 And you might imagine, you know, if -- 8 if a full-term infant has CMV and it's -- it's 9 contracted in utero -- a preterm infant who should be 10 in utero still, but is now being taken care of in -- 11 in the NICU and is born prematurely who contracts CMV 12 might also have some of those same adverse 13 consequences that infants who -- full-term infants who 14 contract congenital CMV might have.</p> <p>15 Many clinicians are actually using 16 antivirals to treat postnatally acquired CMV. They're 17 not approved -- also not approved by FDA for this 18 indication, and not everyone is -- is treating, 19 because I think there's still -- it's still unclear 20 whether this is a disease that benefits from antiviral 21 treatment.</p> <p>22 So therefore, further studies are</p>
<p>1 know, there are some thoughts of -- of where we might 2 go from here.</p> <p>3 So could we use real-world data, so 4 additional evidence from patients who are being 5 treated with -- with congenital CMV now to provide 6 compelling evidence to support changing these drug 7 labels.</p> <p>8 One issue with that is most patients 9 are being treated with congenital CMV. So I think 10 those with symptomatic congenital CMV are -- and are 11 recognized, are being treated, and so it's really hard 12 to know what the natural -- the natural history of 13 untreated participants would be and to really find a 14 great comparison group.</p> <p>15 You know, PTN has thought about can we 16 study something else unrelated and a related diagnosis 17 that might have more equipoise to -- so that we could 18 actually perform a trial in that population.</p> <p>19 And next slide I'll -- I'll end with 20 just some thoughts we have a little bit off of the 21 current topic. But, you know, I think I heard some 22 mention of postnatally acquired CMV earlier. And the</p>	<p>1 needed to determine natural history of postnatal CMV 2 to develop potential trial end points. So a related 3 topic, but just some thoughts of where we might go to 4 study these medications more and that could 5 potentially be applied to the congenital CMV space as 6 well.</p> <p>7 All right. And the next slide is my 8 last. I thank you all for listening to me, and I hope 9 you haven't gotten too hungry in the meantime.</p> <p>10 Thanks.</p> <p>11 DR. HODOWANEC: Thank you, much. Thank 12 you, very much, Dr. Greenberg. Wonderful 13 presentation.</p> <p>14 But we have just a few minutes now. We 15 were supposed to really be starting lunch at this 16 time. Sorry we got a little behind over the course of 17 the morning.</p> <p>18 So we're going to really limit it to 19 just one or two clarifying questions. If it's a 20 meatier comment or question, we'd like to save it for 21 the panel discussion this afternoon.</p> <p>22 Okay. I see that Dr. Bo has his hand</p>

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<p>1 raised. Before I go to you, Dr. Bo, there is one 2 comment in the Q&A box that I would like to read 3 first.</p> <p>4 So we have -- from Alyssa Blake [ph] 5 another -- not a question, but a comment. "Just 6 wanted to, again, thank Dr. Pesch for sharing her 7 perspective and info about congenital CMV.</p> <p>8 I really appreciated her talk and 9 approach to congenital CMV, which focuses on 10 emphasizing supports for children with congenital CMV, 11 rather than cures for neurodiversity and deafness and 12 looking at CCMV as a spectrum, rather than all or 13 nothing, symptomatic versus asymptomatic.</p> <p>14 Her talk was very informative and gave 15 a great nuanced perspective." Yes, Alyssa [ph], we 16 agree wholeheartedly.</p> <p>17 Now, I will turn it to Dr. Bo. Do you 18 have a clarifying question or comment?</p> <p>19 DR. BO: Yes, a quick clarifying 20 question for Dr. Greenberg, and it should be really -- 21 relatively quick, and if we don't have time, I think 22 I'd love to have additional time during a</p>	<p>1 clinically to weigh -- to weigh in on in terms of how 2 often viral levels are -- are followed.</p> <p>3 Certainly, in -- when we had infants 4 with acquired CMV in the NICU, you know, we -- we will 5 sometimes follow viral levels. But I think the 6 evidence and relationship to outcomes is not entirely 7 clear and probably needs to be further elucidated.</p> <p>8 But that's a -- that's a great comment.</p> <p>9 I'm also seeing -- if it's okay, there's a question in 10 the chat that I can address. There's a question about 11 comparing -- a clinical trial comparing another 12 medication, like the letermovir to ganciclovir, and 13 could the PTN support a trial like that.</p> <p>14 And I think, you know, that's -- that's 15 a great question and a potential possibility, I think.</p> <p>16 Certainly, we need to -- we would need 17 to, you know, figure out from a programmatic 18 standpoint of -- you know, particularly, since our 19 focus is mainly on -- on off-patent medications, but 20 if the comparator is something, you know, in an 21 established off-patent medication, that is I think a 22 place where we could explore involvement if there are</p>
<p>1 discussion -- the panel discussion.</p> <p>2 The question is, in the context of 3 congenital CMV, therapeutic area, how well accepted is 4 CMV viremia infection a surrogate marker of disease 5 and poor outcomes?</p> <p>6 I think we've seen that CMV viremia 7 infection was a surrogate and effectively used in the 8 context of a CMV infection posttransplant, either 9 solid or stem cell transplant, but in the context 10 of -- context of -- of CMV, I think this is something 11 worth looking into.</p> <p>12 DR. GREENBERG: That's -- that's a 13 great question and I think probably -- you're right, 14 deserves further discussion in the panel later on in 15 terms of what we're thinking about, whether the trial 16 employs what could -- that could, you know, make 17 something -- these studies a bit more feasible.</p> <p>18 You know, and I invite anyone else, you 19 know, Dr. Kimberlin or whoever, to weigh in as well. 20 But, you know, from an infectious disease expert -- as 21 a neonatologist, this is something that I would 22 definitely be asking my infectious disease colleagues</p>	<p>1 other medications under development for the -- for 2 congenital CMV.</p> <p>3 DR. HODOWANEC: Thank you, Dr. 4 Greenberg, and thank you, Dr. Bo, for that question. 5 I think -- I think there's lots more to be said about 6 that.</p> <p>7 You know, as you pointed out, we really 8 have had a lot of success in the transplant space 9 where we have a lot more comfort with -- with viral -- 10 virologic end points. But I think it's a little 11 different in the congenital CMV space, and I know Dr. 12 Kimberlin will elaborate upon that this afternoon 13 in -- in our panel discussion. So look forward for 14 more to come on that.</p> <p>15 Now, one last comment. I see Dr. 16 Schleiss has his hand raised. This will be the last 17 comment before we go to lunch. Dr. Schleiss?</p> <p>18 DR. SCHLEISS: Yeah, thank you.</p> <p>19 Clarifying question for Dr. Greenberg, whose talk was 20 terrific, by the way.</p> <p>21 I -- I wanted to ask your preemie data 22 or your -- yes, your premature infant valganciclovir</p>

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1 prescription data. I just wanted to clarify. Those 2 are definitely congenital CMV babies that -- that were 3 in your data set?	1 that -- that infant may have had -- may have actually 2 had congenital CMV. 3 So it's -- it's a bit hard to tease out 4 with existing data. But we've -- we've attempted to 5 do that in the past --
4 DR. GREENBERG: Great -- great 5 question. So those were -- it's not -- that 6 particular graph was not just limited to preterm 7 infants. That was all infants with a congenital CMV 8 diagnosis or diagnosis that occurred in the first 21 9 days postnatally.	6 DR. HODOWANEK: Wonderful. Thank you 7 all for the great questions. And -- and thank you, 8 again, to our Session 2 panelists. 9 With this, we will go to lunch, and we 10 will meet back at one o'clock for our -- for our panel 11 discussion. Thank you, everyone.
10 So because it's retrospective data, we 11 couldn't determine unquestionably that this is truly 12 congenital CMV. Not all infants were tested at birth. 13 And so -- but if they were -- it occurred during the 14 first 21 days of -- of age.	12 (Off the record.) 13 DR. HODOWANEK: All right. Welcome 14 back from lunch, everyone. The remainder of our 15 meeting today is dedicated to our congenital CMV panel 16 discussion.
15 DR. SCHLEISS: Okay. So I -- maybe I 16 misread the slide. But I thought -- I thought the 17 slide -- I thought you had one slide that was just for 18 premature infants.	17 As has been highlighted over the past 18 day and a half, the conduct of clinical trials for 19 rare conditions, particularly those involving the 20 vulnerable neonatal population is generally fought 21 with challenges. Trials for congenital CMV infection 22 have their own unique set of challenges.
19 DR. GREENBERG: I did. But the 20 graph -- the graph was for both term and preterm 21 infants.	
22 DR. SCHLEISS: Oh, okay. Well, we can	
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1 talk more about this later. I -- I mean, I think 2 one --	1 Before congenital CMV investigational 2 product can be studied in patients, there are 3 questions regarding CNS and inner ear penetration that 4 must be addressed.
3 DR. GREENBERG: Yeah.	5 Regarding clinical trial design, there 6 are numerous questions regarding patient population, 7 identification of meaningful and feasible efficacy end 8 points and selection of a comparator arm that will 9 provide interpretable data.
4 DR. SCHLEISS: -- discussion is what I 5 perceive frankly to be the overuse of nucleoside 6 antivirals in postnatal CMV infections in the newborn 7 intensive care unit.	10 Over the next several hours, we look 11 forward to robust discussion on these topics and 12 others.
8 So I just wanted to clarify what -- if 9 your data set for the premature babies sorted that 10 out. But we can talk more about it later.	13 While we acknowledge the important 14 potential role of both pre- and postnatal treatment of 15 congenital CMV infection, for the purposes of this 16 workshop, we ask that the primary focus of the 17 discussion be geared towards the development of drugs 18 for the postnatal treatment of congenital CMV 19 infection. Next slide, please.
11 DR. GREENBERG: And that's something 12 that's actually -- I don't think that we've -- we've 13 looked at the incidents of treatment for postnatal 14 CMV -- or we -- I know we haven't published those 15 data.	20 I would now like to introduce the 21 following panelists for the first time. We have Dr. 22 Tien Bo, Global Medical Head of the Transplant and New
16 DR. SCHLEISS: Yeah.	
17 DR. GREENBERG: So it is something that 18 we can look at, of course, the definition of 19 postnatally acquired CMV also has to be, you know --	
20 we -- we might say it's diagnosed after the first -- 21 after the first 21 days of life. But if an infant 22 didn't have testing early in life, it's possible	

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<p>1 Programs at Takeda Pharmaceuticals, and Dr. Paul 2 Griffiths, Emeritus Professor of Virology at the 3 University College of London.</p> <p>4 We also have numerous panelists and 5 speakers rejoining us this afternoon, some of whom 6 presented earlier today and others who presented 7 yesterday.</p> <p>8 Very briefly, our FDA panelists include 9 John Concato, Dr. Lindsay DeVries, Dr. Ryan Kau, Dr. 10 An Massaro, Dr. Lily Mulugeta, and Dr. Kunyi Wu.</p> <p>11 Our external panelists, who have been 12 previously introduced, include Dr. Roberta DeBiasi, 13 Dr. Rachel Greenberg, Dr. David Kimberlin, Dr. Tatiana 14 Lanzieri, Dr. Emma Mohr, Dr. Megan Pesch, Ms. Betsy 15 Pilon, and Dr. Mark Schleiss. We are so excited to 16 have so much expertise and so many unique perspectives 17 represented on this panel. Next slide.</p> <p>18 So the first topic that we would like 19 the panel to discuss this afternoon is the key 20 challenges in antiviral drug development for the 21 treatment of congenital CMV infection.</p> <p>22 So I will -- I know this is a very</p>	<p>1 to humans?</p> <p>2 What's the relationship between the 3 viral load and the severity of CMV -- of CMV clinical 4 manifestations, including the symptomatology?</p> <p>5 And what's the -- the relationship 6 between -- axis -- even longer term treatment on 7 adaptive immunity against CMV that may require a 8 competent immune response to either inoculation 9 challenge or -- or exposure to the virus?</p> <p>10 I think -- to me, I think these are 11 some of the questions that I like to think about when 12 we're thinking about how to extrapolate in the context 13 of the clinical trials and developing new clinical 14 trials.</p> <p>15 DR. HODOWANEC: Thank you for all of 16 those wonderful questions, Dr. Bo. We -- we can take 17 those one at a time, and we might need you to repeat 18 the -- the second two as we go here.</p> <p>19 But I think, you know, starting with 20 your first question about using animal models or -- 21 excuse me, non-clinical studies to help determine 22 whether or not a drug penetrates the -- the human CNS,</p>
<p>1 broad topic. But I just want to start there and see 2 what initial comments some of our panelists might have 3 about what they see as the most significant 4 challenges.</p> <p>5 DR. BO: Aimee?</p> <p>6 DR. HODOWANEC: Yes. Hi, Dr. Bo. 7 Please.</p> <p>8 DR. BO: Hi. Thank you, very much, for 9 that. I think one of the first things that I'd like 10 for us to discuss through that's specific to this 11 first -- number 1 area of focus is actually on the 12 challenge of preclinical models and how could it 13 inform us, even before we start doing clinical trial 14 work in humans.</p> <p>15 And I have a couple of just series of 16 questions. I think I'd just like to ask that, and I 17 think -- let's see how it -- it can be incorporated 18 into the discussion.</p> <p>19 Number 1 is with regards to animal 20 model, Dr. Mohr presented, what's the feasibility of 21 extrapolating the animal model of blood/brain barrier 22 penetration from -- from the macaques or animal models</p>	<p>1 I think, is -- is a great question.</p> <p>2 I don't know if Dr. Mohr has any 3 initial thoughts on that, that she -- she would like 4 to comment on.</p> <p>5 DR. MOHR: Yeah. That -- that's a 6 great question. And I'm not aware of studies that 7 compare the fetal macaque blood/brain barrier directly 8 to human fetal blood/brain barrier studies.</p> <p>9 But I do know that, you know, comparing 10 the fetal neurodevelopment sort of step by step, a lot 11 of that is very similar. And there are some reviews 12 that discuss this about when different -- when 13 different stages happen.</p> <p>14 And a lot of it happens in utero, 15 rather than after birth, like they are in some other, 16 like, hearing models. So that's very prompting as far 17 as long-term exposure during pregnancy.</p> <p>18 DR. HODOWANEC: Thank you, Dr. Mohr.</p> <p>19 Yeah, I think, you know, this is 20 something that we have thought about a fair amount, 21 and -- and one of the other things that comes up 22 sometimes along this line of thinking is that even</p>

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<p>1 within humans that, you know -- what penetrates the 2 human blood/brain barrier at one age might not be the 3 same as -- as at another age.</p> <p>4 And -- and so I think -- I think that 5 this is a really important topic for us to try to -- 6 to understand better.</p> <p>7 Yes. And, Dr. Viswanathan, then you 8 have something to add?</p> <p>9 DR. VISWANATHAN: Yes. This is Prabha 10 Viswanathan. And I just had a follow-up question 11 that's related to this, and this is really to clarify 12 my understanding, Dr. Mohr.</p> <p>13 You mentioned that there -- there seems 14 to be a paucity of studies in -- in the postnatal 15 period and certainly have been in the antenatal period 16 and looking at the fetus.</p> <p>17 I believe Dr. Bo's question was more 18 about the -- the newborn neonate. But it seems, like, 19 there's, again, a paucity of study -- of studies in 20 this population more broadly and -- and curious 21 whether there are any -- any factors that you have 22 seen as -- as being prohibitive, other than the</p>	<p>1 barrier, whether a rhesus macaque correlates with a 2 baby, could we then correlate that with the newborn?</p> <p>3 DR. MOHR: I don't -- I don't know if 4 that answer is out there or -- or available. I think 5 that is a really good question, and I don't know if 6 those studies have been done to look at both fetal 7 blood/brain barrier permeability in the macaque and 8 also in -- in the neonatal macaque.</p> <p>9 Those are good questions. Mark 10 Schleiss has his hand raised, and he's also in this 11 field, and he might -- he might know a little bit 12 about this.</p> <p>13 DR. SCHLEISS: Yeah. I -- I don't -- I 14 don't know the answer to that question, specifically. 15 I mean, my experience is more with rodent models, 16 getting pink models.</p> <p>17 And we -- you know, the newborn mouse, 18 for example, is very much immunologically -- or 19 embryologically like a fetus, and so studying newborn 20 mice might be more relevant to humans in that aspect.</p> <p>21 But I want to step back for a second 22 and just sort of think about the issue of antivirals</p>
<p>1 typical compliment of -- of cost and -- and those 2 kinds of things.</p> <p>3 DR. MOHR: Yeah. So I'll answer the 4 first question first. So what are -- what do I think 5 the factors are that have prohibited studying in 6 infancy congenital CMV infection outcomes and 7 interventions?</p> <p>8 I think the biggest one is the model 9 where you don't get 100 percent penetrant. So when 10 macaque pregnancy studies themselves are, you know, 11 \$25,000 per animal, if you only get 5 out of 12, that 12 actually have congenital CMV infection, how are you 13 going to have large enough sample sizes to test an 14 intervention and see if it works.</p> <p>15 I think that is really challenging, 16 especially when we know that there's a spectrum of 17 congenital CMV disease in -- in infants. I think 18 that's a really large factor here.</p> <p>19 Sorry. I forgot your first question.</p> <p>20 DR. VISWANATHAN: It was just a kind of 21 clarifying question about whether we -- we could -- if 22 we did have some data about a fetal blood/brain</p>	<p>1 and the blood/brain barrier. We heard this morning 2 the comment, which I agree -- agree with, that the 3 damage was already done by the time the baby is born.</p> <p>4 And so, you know, the CISG 112 study 5 did show some preservation of neurodevelopment. 6 But -- but do we really think that antivirals in the 7 infected neonate are having an effect on the infant 8 brain with respect to CMV sequelae, or -- or should 9 our goal really be to try to mitigate ongoing bowel 10 replication in the cochlea?</p> <p>11 And -- and so what do -- what do we 12 hope to gain with antivirals to begin with in terms of 13 neurodevelopmental outcome and congenitally infected 14 babies?</p> <p>15 You know, just thinking about the 16 biology of the virus and the timing of fetal brain 17 infection and the fact that it's almost unheard of to 18 find CMV in the subarachnoid space in a newborn, by 19 that time, has the brain infection already sort of 20 burned itself out and -- and are we really going to 21 gain a lot with antivirals?</p> <p>22 I don't know. Just trying to be a</p>

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<p>1 little provocative here. But curious what the other 2 panelists think about that.</p> <p>3 DR. PICA: Thank you, very much, Dr. 4 Schleiss. In one moment, I'll call on Dr. DeBiasi 5 there.</p> <p>6 I guess sort of one just quick follow- 7 up question that I had to your comments there, you 8 know, we talk about the blood/brain barrier. But I 9 think to your point, one of the things we're 10 particularly interested in is whether or not the -- 11 the drug is getting to the inner ear.</p> <p>12 And so do we need to -- you know, how 13 do we determine that? And so do we need a drug that 14 can penetrate the blood/brain barrier to say that it's 15 reaching the inner ear. Do we know the answer to that 16 question?</p> <p>17 So I will leave that question, and if 18 others have any follow-up comments on that, I -- I 19 would -- would be very interested to hear it. Dr. 20 DeBiasi?</p> <p>21 DR. DEBIASI: Sorry. I just wanted to 22 go back and see perhaps if -- I don't know if Dr.</p>	<p>1 want to be careful about thinking, well, what are 2 the -- what are the deleterious outcomes that could be 3 affected by an antiviral, or if you don't know, be 4 able to at least post-talk look at different aspects 5 of the outcomes. Otherwise, if you just lump 6 everything, you -- you probably lose the effect.</p> <p>7 But I see David is raising his hand.</p> <p>8 So maybe he could tell us a little bit about the 9 virology part of it.</p> <p>10 DR. HODOWANEK: Thank you, Dr. DeBiasi.</p> <p>11 Dr. Kimberlin, we'd love to hear from you on this.</p> <p>12 And then also, Dr. Griffiths would like to comment on 13 some of these viral load related questions as well.</p> <p>14 Go ahead, Dr. Kimberlin.</p> <p>15 DR. KIMBERLIN: Perfect. Thank you 16 for -- for a fantastic morning. And -- and I think 17 the afternoon is going to be really interesting as 18 well as these conversations unfold.</p> <p>19 In my -- my thinking on kind of the arc 20 of the -- of the studies that the CASG and -- and now 21 the Congenital and Perinatal Infections Consortium 22 have undertaken with congenital CMV is that it --</p>
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<p>1 Abzug or Dr. Kimberlin is -- is still on. But could 2 we just summarize what we know about the viral -- you 3 know, the -- the kinetics of the virus in those CSG 4 settings that were done?</p> <p>5 Because, you know, my takeaway from 6 that was, yeah, we suppress the virus, but it comes 7 right back up. But, yet, we still saw this effect.</p> <p>8 So to me, that means that, you know, it 9 may -- there may be some -- antiviral effect is 10 probably important for some aspect of the hearing 11 outcome, but probably not the whole thing or, you 12 know, it wouldn't have been as effective as it was.</p> <p>13 And then, you know, to Mark Schleiss' 14 point, you know -- and I think I said this earlier, we 15 do have to think carefully about what the outcome 16 we're looking at, because the most severe outcome, for 17 instance, following microgyria in a completely 18 structurally abnormal brain, is not going to be 19 affected by antiviral treatment.</p> <p>20 So, you know, we -- we wouldn't want to 21 assess the efficacy of an antiviral treatment by 22 lumping all the outcomes together; right? We would</p>	<p>1 it -- the only way I think you could say that you have 2 the improved hearing outcomes that we see, is either 3 it was just by chance alone or there's an antiviral 4 effect specifically on the inner ear.</p> <p>5 That -- that blood inner ear barrier 6 is -- is where I think the -- the likely activity is 7 happening -- drug getting into the inner ear and 8 having an effect on virus.</p> <p>9 And we know from explants, when people 10 have cochlear implants, at least in a handful that 11 have been looked at, there are some that still have 12 CMV DNA, even in a 5-year-old, a 4-year-old, when 13 the -- when the cochlea is removed, so in -- in the 14 explanted material.</p> <p>15 So I think that the idea of whether 16 it's only that, there could be inflammation as well. 17 There could be a host immune response. I don't know. 18 But -- but I do think it would suggest that there 19 is -- there is active viral replication.</p> <p>20 And at least with respect to 21 ganciclovir and valganciclovir, there is some 22 suppression of that and, hence, the more favorable</p>

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<p>1 outcomes that we saw within the studies.</p> <p>2 I do think we have to think about the</p> <p>3 study designs. It was pointed out, I think, in one of</p> <p>4 the slides -- correctly pointed out that we had a lot</p> <p>5 of loss to follow up in the old ganciclovir treat/no</p> <p>6 treat randomized trial.</p> <p>7 That's a cloud that hangs over that</p> <p>8 study and always will. You can't go back and -- and</p> <p>9 un-ring the bell. But if it -- if -- if what we saw</p> <p>10 in that study was by chance, which I don't think it</p> <p>11 was, but if it -- if it were, then the -- how do you</p> <p>12 explain the 112 study, six weeks versus six months,</p> <p>13 where the longer treatment had better outcomes at a</p> <p>14 year and two years?</p> <p>15 So I -- I think the totality of the</p> <p>16 information is -- building on a series of comments I</p> <p>17 made yesterday, looking at the whole story being told</p> <p>18 across these studies, suggests that there's benefit --</p> <p>19 audiologic benefit -- maybe developmental benefit.</p> <p>20 That was really more of -- that was</p> <p>21 just the 112 study alone. So I -- I'm -- I think</p> <p>22 that's a little bit softer ground personally.</p>	<p>1 example.</p> <p>2 But I want to hear what Paul says,</p> <p>3 because he knows a lot more about this than I do.</p> <p>4 DR. PICA: Thank you, Dr. Griffiths --</p> <p>5 or sorry, thank you, Dr. Kimberlin. Dr. Griffiths,</p> <p>6 would you like to add some comments?</p> <p>7 DR. GRIFFITHS: Yes. Thank you. Let</p> <p>8 me go back to the question that was asked just before</p> <p>9 the break, if there's a possibility of using</p> <p>10 measurements of viral load and the way that they're</p> <p>11 done in the transplant patients.</p> <p>12 If we just go back in history, the stem</p> <p>13 cell transplant patients were being monitored</p> <p>14 increasingly with methods that were becoming more</p> <p>15 rapid, particularly, PCR.</p> <p>16 And so clinicians could note, almost in</p> <p>17 real time, that patients who had viremia pretty</p> <p>18 rapidly went on to get CMV end organ disease, whereas</p> <p>19 the patients who didn't get viremia had a very low</p> <p>20 risk of getting no end organ disease.</p> <p>21 And this led to the interruption of</p> <p>22 preemptive therapy where ganciclovir and</p>
<p>1 In terms of viral load -- blood viral</p> <p>2 load, this has been brought up a couple of times,</p> <p>3 and -- and Dr. Griffiths will be able to -- to put it</p> <p>4 in a broader context with respect to transplant and so</p> <p>5 forth.</p> <p>6 I will mention that Concetta Marsico</p> <p>7 was -- or is an Italian who came and worked with us</p> <p>8 for seven or eight months, something like that, in the</p> <p>9 late 2010s and did a really deep dive into the CASG</p> <p>10 PCR data. And she did find -- and it was, I think, a</p> <p>11 2019 JID paper, she found a statistically significant</p> <p>12 difference where the people that were having worse</p> <p>13 hearing outcomes had higher blood viral loads.</p> <p>14 But there was an awful lot of overlap.</p> <p>15 There were some that had terrible hearing outcomes</p> <p>16 with very low blood viral loads. There were some with</p> <p>17 very high blood viral loads who had normal hearing.</p> <p>18 And so it -- you know, statistically,</p> <p>19 yes, it means something. Clinically, I think it's a</p> <p>20 harder thing to -- I -- I don't think it can be a</p> <p>21 biomarker in the way that, you know, perhaps Dr. --</p> <p>22 Dr. Bo would like for it to be a biomarker for</p>	<p>1 valganciclovir were given in people with viremia to</p> <p>2 stop them getting end organ disease.</p> <p>3 And of course, regulators, like the FDA</p> <p>4 or EMA, will want better data than that to actually</p> <p>5 convince them that this is a reliable marker. And</p> <p>6 extensive trolls of the literature were done to show</p> <p>7 the viral load did, indeed, correct the disease, that</p> <p>8 there were low risks of false positive and false</p> <p>9 negative associations, et cetera. I can find that</p> <p>10 paper and send it back to the -- to the panel</p> <p>11 afterwards.</p> <p>12 And this led to ultimately so called</p> <p>13 "clinically significant CMV infection," being agreed</p> <p>14 as -- as a usable primary end point for phase 3</p> <p>15 clinical trials.</p> <p>16 But it's important to recognize that --</p> <p>17 that is the clinical decision of the clinicians</p> <p>18 looking after those stem cell transplant patients to</p> <p>19 prescribe valganciclovir, which is toxic to the bone</p> <p>20 marrow that they have just engrafted.</p> <p>21 So they only do that if they're really</p> <p>22 convinced -- virtual connectivity interruption --</p>

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<p>1 unilateral hearing loss, a risk factor for getting 2 bilateral hearing loss, because we have to think that 3 their other ear may be being challenged by virus 4 coming in that bloodstream.</p> <p>5 It's obviously not -- not coming 6 directly from one ear into the other ear. It may be 7 going via the bloodstream, and that would be a very 8 doable thing to do in the natural history of study -- 9 doable question to ask.</p> <p>10 Thank you.</p> <p>11 DR. PICA: Thank you, Dr. Griffiths.</p> <p>12 We really appreciate your -- your perspective and 13 providing that additional transplant context.</p> <p>14 I think Dr. Schleiss had his hand 15 raised next. Dr. Schleiss?</p> <p>16 DR. SCHLEISS: Yeah. Yeah, thanks.</p> <p>17 Paul, thanks for that comment. I -- I just wanted to 18 mention a little bit of data that we have that's 19 unpublished. I'm still trying to sort it out.</p> <p>20 But, you know, we were very interested 21 in this universal screening study at the viral load at 22 the time of birth in saliva and dried-blood spot and</p>	<p>1 are in women who have very convincing histories of 2 third trimester primary infections. And those 3 newborns simply haven't had the time to make an immune 4 response to help control their -- their infection.</p> <p>5 They have high viral loads. But they're asymptomatic.</p> <p>6 So I -- I think this is going to end up 7 being complex, and I don't think it's going to be sort 8 of the simple calculus that we see in infectious 9 disease practice where high viral loads usually mean 10 something bad. I don't know that that's going to be 11 the case.</p> <p>12 Now, you brought up an interesting 13 point about systemic viral load and what's going on in 14 the cochlea, and I think that is a little bit of a 15 different situation, because that's an ongoing 16 infection that may percolate for weeks, months, maybe 17 even years.</p> <p>18 One thing I do worry about is 19 compartmentalization in children who have good 20 peripheral viral load control. I don't know that 21 their cochlear CMV strain, if you will, is going to 22 retain susceptibility to ganciclovir.</p>
<p>1 the likelihood of symptomatic disease upon follow-up 2 of these infants.</p> <p>3 Most of the viral load studies in 4 congenitally infected babies have a really strong 5 selection bias, meaning these are the sickest kids, 6 because they are the ones that are identified as 7 having something wrong.</p> <p>8 And so they get an assessment. They 9 have viral load studies done. They're referred to 10 tertiary care centers and clinics. But what -- what 11 do we know from an unselected population?</p> <p>12 And the P value isn't quite 13 significant. But -- but there really does seem to be 14 a trend toward higher viral loads in the asymptomatic 15 babies. And I think I know the reason why. You know, 16 the fetus has an immune system.</p> <p>17 And I think that some of the sickest 18 babies I've seen are the ones that have early 19 gestation infections where the fetal T-cell response 20 has weeks, even months sometimes to kick in and 21 control viral replication, at least to some degree.</p> <p>22 Some of the highest viral loads I see</p>	<p>1 We do know that in both transplant 2 patients and in some congenitally infected infants, we 3 do see compartmentalization of strains that have 4 varying degrees of ganciclovir susceptibility.</p> <p>5 So anyway, just a couple of comments, 6 but I thought I'd share that with the group.</p> <p>7 DR. PICA: Thank you, Dr. Schleiss.</p> <p>8 DR. VISWANATHAN: This is Prabha 9 Viswanathan again. Just one follow-up -- follow-up 10 question, and then we'll turn to you Dr. DeBiasi.</p> <p>11 I'm curious whether there are any data 12 available about whether the cochlea -- the inner ear 13 is -- is a sanctuary site for virus, whether we know 14 if there is an immune response there, whether cells 15 are able to get there -- the immunoglobulin is able to 16 get there and -- and then would -- would a drug be 17 able to get there. We know virus does.</p> <p>18 I see Dr. Kimberlin, you have your hand 19 raised. Please, go ahead.</p> <p>20 DR. KIMBERLIN: I -- I don't know the 21 answer for sure. There are pretty rare instances 22 where a person who had congenital CMV would, usually</p>

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<p>1 when they're in their teenage years, have a very 2 abrupt loss of hearing. Like, they go to bed at night 3 with stable mild hearing loss, and they wake up deaf.</p> <p>4 To me, that -- that would be harder 5 to -- to think of as -- for that example, as a virus- 6 induced hearing loss. It's too abrupt. It sounds 7 immunologic to me. If it is immunologic, then it has 8 to be some sort of immune response in the inner ear 9 where the hair cells are.</p> <p>10 And -- and I would think -- and the way 11 I'm thinking about it anyways, so the implication to 12 me is that, yes, there is an -- there is immunology 13 going on in the inner ear. But I -- I don't know that 14 it's been certainly studied as well as it should, if 15 studied at all.</p> <p>16 DR. PICA: Thank you, Dr. Kimberlin. 17 Dr. DeBiasi?</p> <p>18 DR. DEBIASI: Yeah. I just had a 19 couple other follow-up questions from some of the 20 comments that were just made by Dr. Griffiths.</p> <p>21 So do we have any information about 22 viral loads longitudinally in -- like, you know, we're</p>	<p>1 Are there changes with long-term 2 effects with, you know, continued reinfections? Could 3 that be the case also with CMV?</p> <p>4 So that a congenitally infected child, 5 for whatever reason, if they're one of the few that 6 are very symptomatic and have outcome -- bad outcome 7 either with neurologically or with their hearing, are 8 they actually more susceptible to -- you know, they're 9 going to get exposed to CMV out in the community over 10 time as well, is there something that them, in 11 particular, need to know that would explain repeated 12 infections, you know, making disease even worse?</p> <p>13 Those are just thoughts that came up.</p> <p>14 DR. PICA: Thank you, Dr. DeBiasi.</p> <p>15 It looks, like, Dr. Griffiths has his 16 hand raised to respond.</p> <p>17 DR. GRIFFITHS: Thank you. So to try 18 to address those, the first question, should we be 19 measuring serial viral loads? Yes, I'm sure we should 20 to help understand natural history, first of all, 21 secondly, to get a pharmacodynamic response to the 22 administration of the drug, does the viral load come</p>
<p>1 following them. They have normal hearing -- normal 2 hearing. We're following them clinically over time. 3 I know in the CSG studies, we haven't been able to 4 then, you know, follow viral loads over time and try 5 to correlate that with their hearing loss. So that's 6 just one question.</p> <p>7 The second point was, you know, we're 8 talking a lot about, you know, should viral load be a 9 big part of decisions about designing the next trial.</p> <p>10 To me, it seems, like, you know, if 11 we -- if we believe the studies that have been done -- 12 and I do, that there must be some antiviral effect.</p> <p>13 It seems, like, you know, whether or 14 not we can prove it beyond what has already been done, 15 in practice, people are going to be using antiviral, 16 so maybe we should be focusing more on antiviral, plus 17 or minus other things, to improve the outcome.</p> <p>18 So those were the two points. And then 19 the last thing I was going to ask about if people had 20 thoughts, you know, just like in COVID, we've seen 21 that children who get reinfected may have different 22 outcomes than kids that don't get reinfected.</p>	<p>1 down in, say, the urine or -- or the saliva, and then 2 thirdly, to look for correlations, which may help to 3 understand the pathogenesis of disease.</p> <p>4 If you control the virus load in the 5 urine or saliva, does that correlate with the ability 6 to control hearing loss? And those were put into 7 the -- the last study that David organized in the 8 children age 1 month to 4 years of age. We were going 9 to look for correlates of efficacy -- of outcome.</p> <p>10 Unfortunately, the study didn't show a 11 clinical benefit in hearing loss, so there's no 12 analysis to be done in those terms. But at least 13 there was a reduction in viral load in those 14 biometrical samples.</p> <p>15 And then, you know, second point to 16 that, should we be thinking of adding in something 17 else, like an anti-inflammatory, partly for the 18 reasons that Mark Schleiss has mentioned.</p> <p>19 I think that's really quite 20 interesting, and it would -- certainly is wrong to 21 think of the virus as the bad guy and the immune 22 system is the good guy. They can flip over under</p>

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1 certain circumstances. 2 But can you define what those 3 circumstances are so that you minimize the risk of 4 administering other particular drugs? 5 DR. PICA: Thank you, Dr. Griffiths. 6 Excellent points. 7 Dr. Schleiss? 8 DR. SCHLEISS: Yes. And I -- I just 9 want to weigh -- you know, cast my vote. Definitely, 10 we need to have viral load monitoring as a part of an 11 antiviral study. No question about that. I mean, we 12 need some kind of biomarker to look at whether the 13 antiviral is having an effect. 14 I'm just unsure if the viral load, 15 especially early on in infancy, is a predictor of 16 outcome. But it's a parameter you have to measure. 17 One thing I've always wondered about 18 too is, as in the transplant setting, maybe a little 19 bit of a DNA-emia is a good thing, because it trains 20 your T-cells to help control the infection long-term. 21 But there's a very interesting and I 22 think important paper from Soriano-Ramos, the citric	1 might be able to be developed? 2 Because it really would be extremely 3 helpful, obviously, if we could -- if we could make 4 such an identification. 5 That study should enroll through next 6 year. So hopefully in 2026, we'll begin to have 7 some -- some data from that. 8 DR. PICA: Thank you, Dr. Kimberlin. 9 And can you just clarify, how long is the follow-up? 10 How long are you collecting these samples 11 determinedly? 12 DR. KIMBERLIN: The follow-up is only 13 two years. And that's a whole other issue with -- 14 with respect to the way these -- these studies are 15 funded. 16 You know, what we all want is exactly 17 the point made earlier, we want to know what happens 18 after adolescent, you know, years if possible. But 19 the funding cycles don't allow for that. 20 They'll stretch out five years by the 21 time you write the protocol, get the study enrolling, 22 have time to clean the database, analyze, do your
1 study in Spain that's just -- just came up on PubMed 2 three, four days ago, in which they looked at 3 interferon gamma CD8 and CD4 responses in infants with 4 congenital CMV and didn't find any correlation between 5 CMV specific CD4 and CD8 T-lymphocyte responses and 6 long-term sequelae. 7 So although I think that's another 8 parameter we need to look at, it doesn't appear that 9 the education of T-cells in the congenitally affected 10 infant is a predictor of sequelae of either. 11 DR. PICA: Thank you, Dr. Schleiss. 12 Dr. Kimberlin? 13 DR. KIMBERLIN: I'll just mention that 14 we do have a study that was started when we still 15 called ourselves the CASG, a CMV biomarker study, 16 that -- where we're -- we're hoping -- we're going to 17 be looking at a -- or we are looking at a number of 18 different things, transcriptomic, cell mediated, 19 humeral viral load. 20 And -- and the idea there hopefully 21 would be with -- if -- if no one of those is a single 22 biomarker, could there be a composite biomarker that	1 final study reports. 2 It's -- it's an artificial framework 3 that we put on what is a natural process from the 4 virus and the host. 5 We do have -- and -- and I -- I dashed 6 away during lunch and saw one of our study subjects. 7 We have a follow-up study, one of the CPIC studies, 8 bringing people back who had been treated as an infant 9 for congenital CMV. 10 And of course, they're going to be 11 anywhere from, you know, 4 years of age or, you know, 12 6 years of age, something like that, out to the 15- 13 year-old and older that I saw today to see whether -- 14 mostly what the durability of hearing is. 15 That's going to be sort of, I think, 16 discernable. It's not -- it's a -- it's a one-time 17 visit. So it's going to -- there will be some 18 weaknesses to it. 19 Also, what their development is and 20 what's happened with respect to any toxicities. You 21 know, have they entered puberty as would be expected, 22 for example? Have they had any kind of cancers?
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<p>1 Because as we know, ganciclovir in animal -- some 2 animal models can be carcinogenic.</p> <p>3 So -- so we'll have some additional 4 data there. But it's not the same as following the 5 same cohort sequentially over many years. That's 6 simply not feasible, at least with the funding 7 mechanisms we've been able to identify so far.</p> <p>8 DR. PICA: Thank you, Dr. Kimberlin.</p> <p>9 Dr. DeBiasi?</p> <p>10 DR. DEBIASI: Yeah, I -- I'm excited to 11 hear about that, and that was actually going to be my 12 next question is, do we have planned or have we done 13 any kind of cytokine, proteomics, transcriptomics 14 analyses, but not just of the severely affected kids, 15 but a comparator to the asymptotically affected 16 kids?</p> <p>17 Because as always, there's a big amount 18 of noise when you're trying to find those biomarkers, 19 and having that control group is important, if you 20 can. So just curious about that too.</p> <p>21 DR. KIMBERLIN: Yeah, that's an 22 excellent question. And Octovio Ramios' [ph] group</p>	<p>1 this. It's from Laura Gibson.</p> <p>2 "In general, antimicrobials work best 3 as a support for the immune system, which in children 4 has variable capacity, depending on gestational or 5 post -- postnatal age.</p> <p>6 Could we use therapeutic vaccines or 7 other immune based therapies for infants or even 8 fetuses with or without antivirals? I think this 9 would be an important approach to study."</p> <p>10 We wanted to share this concept as we 11 were talking about adjunctive strategies to 12 antivirals. I do think that these immune based 13 therapies and therapeutic vaccines are a little bit 14 out of scope of this conversation, but did want to 15 share this idea with the group, because I think it's a 16 great point.</p> <p>17 DR. PICA: Thank you.</p> <p>18 Dr. Bo, so I think we've covered your 19 first question and your second question. But can you 20 remind us your third question? Have we tackled that 21 one yet?</p> <p>22 DR. BO: Yes. No. Thank you, very</p>
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<p>1 has done some of that work with both what we -- I 2 don't know if we're going to keep calling them 3 "asymptomatic" and "symptomatic" -- I'm not sure what 4 the terminology will be, but using that older 5 terminology, they've done -- Asumit Haes [ph] has done 6 beautiful work.</p> <p>7 Nature's -- one of the nature journals 8 published it, with identifying a transcriptomic 9 signal -- seven genes if I remember correctly.</p> <p>10 And, well, that's -- we're partnering 11 with her on the biomarker study to -- to be able to 12 hopefully have some application of that to a test 13 population, not just a development population.</p> <p>14 I -- I want to clarify something. I 15 think I said out to two years for biomarker. It's 16 going to be out to -- for some of the subjects -- 17 those enrolled farther back, out to 3 years of age. 18 But still, not out to 8 years, 9 years, 10 years of 19 age, like we really would like.</p> <p>20 DR. PICA: Thank you, very much.</p> <p>21 DR. VISWANATHAN: There's one comment 22 in the Q&A that we'd like to share, and I'll just read</p>	<p>1 much. And actually, on the lines of -- I think one of 2 the questions -- I think any -- involving small babies 3 is the small volume of tissue and blood that you can 4 expect --</p> <p>5 DR. HODOWANEC: Dr. Bo, I'm sorry. 6 We're having a hard time hearing you.</p> <p>7 Are others having difficulties as well, 8 or is it our connection? Others are as well. Okay.</p> <p>9 DR. BO: Let me -- let me -- yeah, can 10 you hear me now? Better?</p> <p>11 DR. HODOWANEC: Yes, that's better.</p> <p>12 DR. BO: Perfect. Thank you. In 13 essence, one of the challenges associated with 14 conducting clinical trials is collecting blood or 15 tissue samples from small babies.</p> <p>16 And so the question that I have for the 17 panel to -- I'd love to -- to, of course, to discuss 18 through this, what are the clinical feasibility and 19 medical justification considerations on the 20 prioritization of required blood draws or tissue 21 samples or cerebral spinal fluid collections and 22 burden on babies in this patient population?</p>

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<p>1 DR. HODOWANEC: Excellent question, Dr.</p> <p>2 Bo. I think everybody is thinking about it in their</p> <p>3 minds.</p> <p>4 Please, feel free to raise your hand if</p> <p>5 you have something to add.</p> <p>6 DR. KIMBERLIN: I don't have -- well, I</p> <p>7 know what the -- the parameters are. It's 3 -- 3 mLs</p> <p>8 per kilogram over 24 hours or 7 mLs per kilogram over</p> <p>9 six weeks, depending on local IRB versus NIH</p> <p>10 guidelines and so forth.</p> <p>11 I will say -- and FDA, please, you</p> <p>12 know, weigh in with what -- if you all have parameters</p> <p>13 I'm not aware of.</p> <p>14 If you -- if you look back at CASG</p> <p>15 studies -- and this could be neonatal herpes or -- or</p> <p>16 the neonatal enteroviral sepsis or the congenital CMV</p> <p>17 studies, we have in the method section what the</p> <p>18 minimum weight is, and there's nothing magical about</p> <p>19 it, except it's a measure of blood out.</p> <p>20 How much can we -- what -- what's the</p> <p>21 lowest weight that we can enroll and -- on that 3 per</p> <p>22 kilo or 7 per kilo, whichever we're looking at, not</p>	<p>1 swinging back toward increased risk.</p> <p>2 There was this paper, of course, that</p> <p>3 got a fair bit of attention in Genome Medicine -- I</p> <p>4 put it in the chatroom, on ganciclovir induced</p> <p>5 mutations following various transplantation settings,</p> <p>6 which I don't know if that has percolated out into the</p> <p>7 pharmacy circles or if -- of -- or if this is just</p> <p>8 anecdotal.</p> <p>9 I mean, again, I just -- I haven't</p> <p>10 heard much about this in many -- many years. And it</p> <p>11 seems to be on the radar now of our local pharmacies.</p> <p>12 So I wondered if others had this</p> <p>13 experience, if you had any comment on this from a</p> <p>14 regulatory perspective, Dr. Greenberg, and from a</p> <p>15 scientific perspective, is this really something we</p> <p>16 really need to worry about?</p> <p>17 DR. GREENBERG: Yeah. Thank you for --</p> <p>18 thank you for sharing. I hadn't -- I hadn't seen that</p> <p>19 article before.</p> <p>20 But I think it underlies this potential</p> <p>21 long-term risk and the importance of studying any</p> <p>22 medications in infants and children, because the --</p>
<p>1 take out more for research related labs in that</p> <p>2 threshold?</p> <p>3 So it has a direct impact on the way --</p> <p>4 on the decision on who gets to enroll in the studies.</p> <p>5 DR. PICA: Thank you, Dr. Kimberlin.</p> <p>6 Dr. Schleiss, did you have something</p> <p>7 you would like to add?</p> <p>8 DR. KIMBERLIN: Well, at the risk of</p> <p>9 shifting topics for a second. But I did want to just</p> <p>10 sort of go back to this issue of the carcinogenicity</p> <p>11 of ganciclovir, which I -- I don't think is really a</p> <p>12 big issue, but maybe -- maybe Dr. Greenberg has a</p> <p>13 comment on this.</p> <p>14 You know, we've been seeing some of our</p> <p>15 pharmacies in the Twin Cities starting to raise this</p> <p>16 issue, and to the point of this should be treated like</p> <p>17 you would treat chemotherapy; the parents need to wear</p> <p>18 gloves before they try to administer the medication.</p> <p>19 It's sort of <i>đbjđ vu</i> all over again,</p> <p>20 because I remember this stuff being discussed 15 years</p> <p>21 ago, and then I -- I really haven't heard much about</p> <p>22 it for a long time. But now the pendulum seems to be</p>	<p>1 the length of time after exposure that they have to</p> <p>2 experience adverse effects, even long-term adverse</p> <p>3 effects, is -- is substantial.</p> <p>4 So, you know, you -- you bring up a</p> <p>5 very important point, and the reason why it is</p> <p>6 important to do -- to do these -- to do these studies.</p> <p>7 Now, to -- you know, I think it -- it</p> <p>8 highlights the importance of sort of that post</p> <p>9 marketing follow-up and how, you know, we could put</p> <p>10 together, you know, their different ways to -- to do</p> <p>11 that.</p> <p>12 But, you know, should every -- every</p> <p>13 patient who -- who is being prescribed this, you know,</p> <p>14 could we -- could we have a registry? Could we have</p> <p>15 something so that we could capture these data more</p> <p>16 symptomatic -- more systematically?</p> <p>17 And I think it -- it also, I think,</p> <p>18 highlights the reason why, you know, we have these</p> <p>19 stops in -- in place of, you know, why there is such a</p> <p>20 burden of -- of proof for safety and efficacy to get</p> <p>21 something into the -- into a drug label.</p> <p>22 I don't know whether this is the thing</p>

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1 that -- you know, weighing risk and benefit, that 2 that's the -- you know, that this is enough of a risk 3 to -- to be a concern.	1 about these side effects. We're really worried." 2 What -- you know, asking the group kind of what -- 3 what would they do.
4 But it certainly leads one to stop and 5 think, particularly in the postnatally acquired CMV, 6 which again, is a totally -- you know, it's a 7 different topic.	4 A few people have popped up with 5 pictures of their prescription bottles with the 6 chemotherapy kind of label on it -- I remember my 7 daughter had that on hers as well, and, you know, 8 asking kind of for group consensus, because I think 9 there's a lot of confusion.
8 But there are some places that for 9 certain patients with what appears to be symptomatic 10 postnatally acquired CMV, that they're -- they're 11 treating with these medications. And so I think -- I 12 think it -- it's all important points. I don't think 13 I have an answer. But interest -- interested in what 14 others think as well.	10 So, you know, if the label should be 11 there, and if that is the safe thing to do, then 12 that's one thing. But it certainly is adding to a lot 13 of anxiety if -- if it isn't warranted, so hard to 14 say.
15 DR. SCHLEISS: From a practical 16 perspective, do -- do parents need to be wearing 17 gloves and treating this as a chemotherapy?	15 DR. SCHLEISS: I've had parents refuse 16 therapy, Megan, precisely for this reason.
18 And -- and I just want to echo your 19 other point about the importance of registries. There 20 is an association between congenital cytomegaly virus 21 injection and acute lymphoblastic leukemia in 22 childhood, an unproven association I might add.	17 DR. PESCH: Yeah. 18 DR. SCHLEISS: For babies that really 19 should have been treated. 20 DR. PESCH: Right. Yes. 21 DR. HODOWANEC: Very interesting. 22 Thank you, all. Anybody have any additional comments
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1 But -- but it just shows you how 2 complex this is going to be unless it's really 3 carefully dissected out in perspective studies.	1 on -- on this topic, the -- the -- you know, the 2 greatest challenges or additional preclinical, 3 nonclinical work that could be done before we move 4 into question number 2 for this first panel session?
4 DR. PICA: Thank you, all. 5 Dr. Pesch, I'm wondering, you know, 6 this discussion about, you know, whether people who 7 are receiving ganciclovir, if ganciclovir needs to be 8 treated like chemotherapy. You know, you had talked a 9 lot about other CMV parents talking about their 10 experiences with being treated, like, you know, that 11 they were very contagious and all of these 12 precautions.	5 DR. MOHR: I wanted to add something to 6 the discussion on the -- the really long long-terms of 7 antiviral exposure.
13 Have you heard anything to that effect 14 regarding treatment or more infectious concerns? Is 15 this something that -- that comes up within the -- the 16 patient and parent community?	8 And I wonder -- you know, doing studies 9 on this now sure will get answers in 20 years. But 10 that doesn't answer the question immediately for 11 people that want to know.
17 DR. PESCH: Yeah, it comes up quite a 18 bit. I mean, families are -- are often overwhelmed 19 with the worries of, I think, carcinogenicity and 20 also, like, fertility concerns as well.	12 And I wonder if, you know, looking in 13 electronic health records retrospectively could give 14 signals to something like this.
21 So we often have -- I see families 22 popping up, saying our -- you know, "We -- we talked	15 And no -- obviously, no individual 16 healthcare system is going to have the numbers 17 required to do this, but something that, you know, 18 combines multiple electronic healthcare systems. 19 I know the -- the electronic health 20 system Epic has -- you know, combines all -- all 21 systems together in a huge research database that you 22 can access when you pose some special questions called

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<p>1 the "Cosmos."</p> <p>2 And you can get access to, you know,</p> <p>3 deidentified data through all of this, but they have a</p> <p>4 research team where they can ask these sort of</p> <p>5 questions.</p> <p>6 It's really interesting the different</p> <p>7 work that they can do. But you could somehow figure</p> <p>8 out how to pose a question. Like, over the last ten</p> <p>9 years as babies have been prescribed valganciclovir,</p> <p>10 are there more signals for, you know, childhood onset</p> <p>11 oncologic diagnoses? And I would imagine that's</p> <p>12 something that their database may be able to do.</p> <p>13 DR. BO: Yeah. As exciting as that may</p> <p>14 seem, I think one of the -- you know, the challenges</p> <p>15 Mark -- Mr. Schleiss mentioned, which is there are</p> <p>16 viruses that have the potential to be oncogenic.</p> <p>17 On top of that, I think the patient</p> <p>18 population is so heterogeneous. Even in transplant,</p> <p>19 we see that it's not only the patient's primary</p> <p>20 disease that contribute to oncogenic potential, but</p> <p>21 it's also polypharmacy multi-medications.</p> <p>22 Immunosuppressive agents is also</p>	<p>1 heterogeneity, unfortunately, of the CCMV itself and</p> <p>2 all the various attributes that we've heard about</p> <p>3 today.</p> <p>4 So, you know, electronic health records</p> <p>5 are helpful. But we don't fault the clinicians for</p> <p>6 not recognizing that the data might be pulled later</p> <p>7 for research of protocol.</p> <p>8 And in a different context, I often</p> <p>9 say, you know, we're not talking about randomized</p> <p>10 trials right now. But randomized trials are wonderful</p> <p>11 for two reasons. One is randomization. The second is</p> <p>12 the protocol that dictates the high-quality data</p> <p>13 that's collected, and that's hard to come by</p> <p>14 retrospectively. Although, it should be explored or</p> <p>15 can be explored.</p> <p>16 DR. PICA: Thank you, Dr. Concato.</p> <p>17 Appreciate your perspectives. Well, we only have a</p> <p>18 little less than 15 minutes in this first panel</p> <p>19 session.</p> <p>20 So I'd like to at least briefly turn</p> <p>21 our discussion towards the second topic, which is</p> <p>22 discuss the potential strategies that could be</p>
<p>1 relationship -- in connections with oncogenic</p> <p>2 potentials. Hence, I think the complexity of the so</p> <p>3 many different factors might require a greater</p> <p>4 intelligence.</p> <p>5 DR. PICA: Thank you, all, very much.</p> <p>6 Oh, I see Dr. John Concato has -- thank you, very</p> <p>7 much.</p> <p>8 And so for those of you who were not</p> <p>9 able to join us yesterday, Dr. Concato gave a</p> <p>10 wonderful presentation on the potential role of real-</p> <p>11 world evidence for -- for these two conditions that</p> <p>12 we're discussing at this workshop.</p> <p>13 Dr. Concato?</p> <p>14 DR. CONCATO: Yeah, I agree with the</p> <p>15 last two comments -- or the question and the response,</p> <p>16 that while it's theoretically possible to look in</p> <p>17 electronic health records, the complexity is not only</p> <p>18 considerable, it's -- it's daunting.</p> <p>19 Not to throw up one's hands in advance</p> <p>20 before trying, but there is heterogeneity across</p> <p>21 healthcare systems. There is heterogeneity within the</p> <p>22 healthcare system, and that's before we get to the</p>	<p>1 considered to improve collaboration between industry,</p> <p>2 academia, and parent caregivers to facilitate</p> <p>3 antiviral therapeutic development for the treatment of</p> <p>4 congenital CMV infection.</p> <p>5 And I'll throw in there even that in</p> <p>6 addition to that, also collaboration -- potential</p> <p>7 legislative work, the base of some of our talks that</p> <p>8 we heard this morning as well.</p> <p>9 What -- what additional collaborations</p> <p>10 could help move -- move the field forward?</p> <p>11 DR. BO: You know, on this part, I just</p> <p>12 need to get something out there really quick, just to</p> <p>13 admire Dr. Pesch's passion behind her presentation of</p> <p>14 this and how moving it was for me to hear Dakota's</p> <p>15 story.</p> <p>16 And Dakota's story of -- the issue of</p> <p>17 liability comes in so much that in some ways, it's --</p> <p>18 it's a really challenging barrier for, I think,</p> <p>19 patients for industry, for regulators, and for the</p> <p>20 legal system to try to reconcile with.</p> <p>21 It's such a big issue that I think if</p> <p>22 somehow there is an agreement on this front, it could</p>

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<p>1 really unleash a lot of the innovation in this space 2 because of the -- the -- that this barrier is removed. 3 DR. PICA: Thank you, Dr. Bo. 4 Dr. Kimberlin? 5 DR. KIMBERLIN: So focusing on -- on 6 question number 2, I spent about three years working 7 with Roche gratis, no -- no compensation or anything, 8 just -- just trying to help as they interfaced with 9 FDA to try to get a breakthrough designation status or 10 an orphan drug status for valganciclovir, as I recall. 11 And -- and the -- ultimately, that -- 12 they pulled out of that process, because at least my 13 recollection is that what was proposed back is that we 14 would have to do another phase 3 study. 15 So to some extent, I think this is a 16 very appropriate question to have. I would add in 17 there, in addition, what could FDA do to -- to 18 facilitate industry having a path forward in a timely 19 enough fashion. 20 Especially thinking about valgan and 21 ganciclovir, these are all patent. I mean, these -- 22 they had -- they were just doing this out of -- truly</p>	<p>1 industry perspective regarding strategies that could 2 help enhance or accelerate the transfer -- the 3 investments in the space to produce -- transport the 4 medicines for patients would be, I think, something 5 that is already -- is in existence, and that is the 6 accelerated review pathway and then the full approval 7 pending confirmation of clinical benefit. 8 I think that's something that could -- 9 could be reminded and potentially discussed in -- in 10 ways of how primary -- the selection of primary 11 outcomes for clinical trials could also be integrated 12 into the accelerated approval pathway. 13 DR. PICA: Thank you, Dr. Bo. We -- we 14 definitely will be talking about end points as a large 15 part of -- of the second panel session. And I 16 understand sort of all of these topics are so 17 intertwined it's hard to really compartmentalize these 18 discussions. 19 But we will certainly be talking 20 about -- about potential end points, and we can have 21 additional discussions about potential accelerated 22 approval pathway.</p>
<p>1 out of the goodness of their heart. They didn't have 2 anything left to -- to gain from it, at least not that 3 I could see. 4 So I think that has to be part of the 5 conversation as well. And I'm going to stop there for 6 right now. I have another -- another comment that 7 I -- I'd like to see if that gains any traction from 8 conversation here. 9 DR. PICA: Thank you, Dr. Kimberlin. 10 I would just briefly say before we open 11 it up to other panelists to respond to your comments, 12 you know, we really are not able to engage in any 13 product specific conversations here, which I 14 understand is very challenging, given the large role 15 that valganciclovir and ganciclovir play in the 16 current landscape. 17 But in terms of the development program 18 for any specific product, we at least, as -- as the 19 agency, are not going to be able to -- to go down that 20 path today. So I will stop there and see what other 21 comments people might have. 22 DR. BO: Something really quick from an</p>	<p>1 Again, I think we've heard a lot of 2 hesitation regarding a virologic surrogate end point 3 based on the data that is available. But -- but we 4 can certainly have -- have further discussions about 5 that. 6 Dr. DeBiasi? 7 DR. DEBIASI: I was just going to ask 8 if, you know -- getting to the point here about how 9 can parents and caregivers play a role here to improve 10 collaboration, have there been any PCORI studies to 11 just identify what are the -- the highest priority 12 concerns of the target patient population in families? 13 I was involved in some of those for 14 Kawasaki disease studies in the last five years, and 15 it's actually very -- very interesting to -- to see 16 that there's not always complete alignment between 17 what we think people want us to study and what they 18 actually would like us to study. 19 So I was just curious if that's been 20 looked at in a PCORI-like way for congenital CMV. 21 DR. PICA: Thank you, Dr. DeBiasi. 22 Dr. Pesch, I see you have your hand</p>

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<p>1 raised.</p> <p>2 DR. PESCH: Yeah. I think there were a 3 couple of PCORI studies funded well over ten years 4 ago. But nothing has made it to publication, and I -- 5 I agree, it's high time and low hanging fruit in terms 6 of opportunity for funding.</p> <p>7 I think over the last ten years, the 8 National CMV Foundation has been around for ten years 9 now. CMV Canada is growing. There's CMV Action in 10 the U.K.</p> <p>11 And so these family organizations, I 12 think, have really grown and are picking up momentum 13 and very eager to collaborate.</p> <p>14 I'm -- I'm always just so blown away by 15 the -- the generosity of these families. I just 16 wrapped up a study of 300 CMV families, and everybody 17 did it for a sticker and a thank you card -- like a 18 bumper sticker and a thank you card.</p> <p>19 They're very eager, I think, to help in 20 the next generation and, you know, those yet to be 21 born. So I think that's one way to really increase 22 collaboration is just to ask.</p>	<p>1 that will be really needed to propel this forward and 2 something that we, as a community, can discuss as an 3 avenue for next steps as well.</p> <p>4 But I do know we are -- our clock is 5 ticking down, so let us turn it back over. Dr. 6 DeBiasi, please, go ahead.</p> <p>7 DR. DEBIASI: Oh, I just -- I was going 8 to follow up to Dr. Pesche -- Pesch. I'm sorry. I'm 9 saying your name wrong.</p> <p>10 Do you have a sense -- just I know 11 there are all these mechanisms to formally assess, you 12 know, what patients want. But, you know, since you're 13 in that, interfacing with those groups and part of 14 that, do you have a sense of, like, what is the hot -- 15 like, what is -- what do people most want?</p> <p>16 DR. PESCH: Well, it's not hearing loss 17 that they're most concerned about.</p> <p>18 DR. DEBIASI: Right.</p> <p>19 DR. PESCH: And not to discount the 20 hearing loss or the impact --</p> <p>21 DR. DEBIASI: Right.</p> <p>22 DR. PESCH: -- but honestly, so often</p>
<p>1 DR. VISWANATHAN: Thank you, so much, 2 for those comments.</p> <p>3 And before we go back to Dr. DeBiasi, 4 Dr. Kimberlin, I just want to note that FDA is -- is 5 really very invested in getting the feedback of -- of 6 patients and caregivers to -- to talk about what is 7 truly clinically meaningful, because we academically 8 have an idea of what is -- is the most powerful end 9 point or the most impactful end point.</p> <p>10 But it doesn't always align with really 11 what families are looking for. As Dr. Hodowanec 12 already mentioned and -- and Dr. Pesch mentioned, we 13 had convened earlier a patient listening session, 14 which gives FDA the opportunity to hear from a small 15 number of patients really about their clinical -- 16 their experience, their stories.</p> <p>17 And we also have a mechanism called a 18 "Patient-Focused Drug Development Program," which is 19 more formal and allows for a larger venue and a larger 20 audience for participation and can be attended by 21 patient advocacy groups, individual patients, 22 professional societies, many of the key stakeholders</p>	<p>1 I'll talk to families, and we're all, like, "Oh, well, 2 it's just hearing loss." Like, the MRI is clean. So 3 far, it's just hearing loss.</p> <p>4 So I think it's those kids that have 5 the -- I mean, I think probably the biggest topic are 6 those kids that are -- have kind of the mild CNS 7 involvement, the white matter, the 8 lenticulostriate vasculopathy that no one really knows 9 quite what to do with.</p> <p>10 And then later on, it's the gross motor 11 stuff, the kids who can't -- who struggle with ADLs 12 and independence. And then intertwined with that, we 13 just see so much with autism. And I do --</p> <p>14 DR. DEBIASI: Yeah, and I -- that -- 15 that's exactly what I was expecting to hear, just from 16 talking to my own patients that -- not that all the 17 work that we've already done is not important. But it 18 might be time to reassess, like, what it is that we 19 actually want to focus our energy on.</p> <p>20 Because I think those things you just 21 said are the things that are -- people are most 22 concerned about and that we have the least information</p>

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<p>1 about.</p> <p>2 And we don't, you know -- we have</p> <p>3 cochlear implants. We don't have ways to fix unknown</p> <p>4 white matter, you know -- so I think that's a really</p> <p>5 important point.</p> <p>6 DR. PICA: Yes. Thank you, Dr. Pesch.</p> <p>7 I -- I think, you know, that -- that makes a lot of --</p> <p>8 a lot of sense. And I think it really helps us sort</p> <p>9 of frame some of our ongoing discussions about end</p> <p>10 points in this next session here. But it's such a</p> <p>11 really helpful perspective for us to have. Thank you.</p> <p>12 So we are almost at breaktime. We will</p> <p>13 hear briefly from Dr. Kimberlin and Dr. Bo, and then</p> <p>14 we will be going to break.</p> <p>15 DR. KIMBERLIN: And -- and mine is a</p> <p>16 deflection to Dr. Greenberg. I'm -- I'm interested</p> <p>17 in -- in the PTN and C-Path efforts from a couple of</p> <p>18 years ago. And then I stopped hearing about it with</p> <p>19 respect to valganciclovir and an indication.</p> <p>20 DR. GREENBERG: Yes. Thanks. Thanks,</p> <p>21 Dr. Kimberlin. I -- we, you know, had engaged with</p> <p>22 you to find out everything that you had gone through</p>	<p>1 signals from a regulatory standpoint were that it was</p> <p>2 going to be hard to get to the level of evidence that</p> <p>3 was needed, which is sort of that well controlled</p> <p>4 efficacy trial.</p> <p>5 So we just kind of ended up in a</p> <p>6 standstill. That's where we started pivoting, you</p> <p>7 know, our focus to maybe -- maybe postnatally acquired</p> <p>8 CMV; there's something we can -- we can do there.</p> <p>9 But it still leaves us just with a bad</p> <p>10 stuck feeling of, you know, how -- how is, you know --</p> <p>11 how is the entire clinical community that takes care</p> <p>12 of these infants and parents kind of on one -- in one</p> <p>13 place and a agency at the -- in a different place.</p> <p>14 But I understand the -- the perspective</p> <p>15 as well. So --</p> <p>16 DR. PICA: Thank you, Dr. Kimberlin and</p> <p>17 Dr. Greenberg. Dr. Bo, just briefly, and then we'll</p> <p>18 go to break. Thank you.</p> <p>19 DR. BO: Yes, very briefly. I think</p> <p>20 the lack of feasibility is a back breaker for</p> <p>21 pharmaceutical companies trying to invest in</p> <p>22 developing drugs.</p>
<p>1 and to see whether -- because PTN has this special</p> <p>2 pathway by which we can pursue changes to drug labels</p> <p>3 outside of the -- the industry space; right? So we</p> <p>4 have this -- this way to engage with FDA and introduce</p> <p>5 these label changes.</p> <p>6 But I think we encountered the same</p> <p>7 barriers that -- that you had, and that's where I</p> <p>8 brought up those -- the -- you know, the issues of</p> <p>9 previous studies, although totally agree with you from</p> <p>10 a clinical standpoint, and almost all neonatologists,</p> <p>11 I think, are in agreement that for moderate to severe</p> <p>12 congenital CMV, that there's a -- that there's a net</p> <p>13 benefit to -- to treatment, and that's why you see</p> <p>14 everyone being treated.</p> <p>15 Although, there -- you know, there is</p> <p>16 no indication. And there -- there seem to be an</p> <p>17 insurmountable barrier for us to be able to -- to use</p> <p>18 just existing data to help pursue a regulatory change.</p> <p>19 Now, we -- we did -- we did have a lot</p> <p>20 of -- we did have other discussions regarding how</p> <p>21 real-world data might help to add to the body of</p> <p>22 evidence and would -- better preliminary, I guess,</p>	<p>1 And I think what the Pediatric Trial</p> <p>2 Network and what you're doing, Dr. Greenberg and</p> <p>3 advising others, is really amazing.</p> <p>4 Yet, I also wanted to quickly add to</p> <p>5 the question for which we can think about later</p> <p>6 following the meeting, which is how can we incorporate</p> <p>7 data digital and new technology that seems to connect</p> <p>8 us all over the world?</p> <p>9 You know, with the -- with this</p> <p>10 technology, how can that -- how can that be leveraged</p> <p>11 further to try to connect with underserved</p> <p>12 communities, to try to connect with rural communities</p> <p>13 across the U.S. -- across the world, have better</p> <p>14 access to clinical trials, which are needed to enhance</p> <p>15 the feasibility, therefore, bring new drugs into the</p> <p>16 market?</p> <p>17 And we often -- I can tell you that the</p> <p>18 experience of running different clinical trials is the</p> <p>19 lack of feasibility and when we hear about patients</p> <p>20 who have a condition that will qualify for the study.</p> <p>21 Yet we also hear at the same time,</p> <p>22 well, that they're not part of the study; they're not</p>

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<p>1 even close to a participating trial center, and our 2 hearts and -- and stomachs are wrenched about not 3 being able to provide access, just simply because 4 there isn't -- there's a major gap between data 5 digital and technology, allowing for the satellite 6 sites, you know, for these mechanisms to offer the 7 extension of the study to those underserved 8 communities.</p> <p>9 DR. GREENBERG: So really, that's a 10 really great point, and I think, you know, the 11 complexity of the types of studies that need to be 12 done under regulatory guidance, you know, does limit, 13 you know, in some ways how -- how many -- how many 14 sites can engage.</p> <p>15 It's -- there's a cost barrier.</p> <p>16 There's a -- a, you know, ability and experience 17 barrier. But, you know, I think opening our minds to 18 other types of studies and what kind of data could be 19 used to support labeling, indications, post marketing 20 evidence is -- is really key.</p> <p>21 So thinking about what -- can we take 22 advantage of, you know, maybe not -- maybe not totally</p>	<p>1 question, the FDA has published a guidance on 2 decentralized clinical trials.</p> <p>3 I'm not suggesting that this current 4 context is amenable. But I think we'll pick up after 5 the break with a lot of these issues, likewise, to Dr. 6 Greenberg.</p> <p>7 It's not that we are slamming the door 8 on other avenues, other approaches, but it's -- the 9 devil is in the details.</p> <p>10 So thank you.</p> <p>11 DR. PICA: Thank you, everyone.</p> <p>12 Wonderful discussion. I hate to -- to cut it short.</p> <p>13 But we do want to make sure we get at least a brief 14 break in here. So we will -- we will take a quick 15 break and meet back at 2:15. Thank you, everyone.</p> <p>16 (Off the record.)</p> <p>17 DR. HODOWANEC: All right. Welcome 18 back from break, everyone. We will now begin our 19 final session of the workshop. Hard to believe it's 20 coming to an end.</p> <p>21 So for this second half of our 22 congenital CMV panel discussion, we would like to talk</p>
<p>1 retrospective EHR data, but sort of a registry format, 2 or a lot of the -- a good number of the studies we do 3 in PTN are opportunistic. So, you know, you saw all 4 the sites on our -- on our map.</p> <p>5 Many of them are participating in 6 studies where the children -- children and infants are 7 involved when they're receiving these medications. 8 But as part of standard care, they're not enrolled as 9 an intervention. They're enrolled -- so it's a 10 simpler study.</p> <p>11 It's more of a data collection and 12 maybe some by a specimen collection, which does 13 require expertise as well.</p> <p>14 But there's -- there may be ways to 15 think about what kind of study design, and that would 16 probably take us into the next hours as well. 17 Would --</p> <p>18 DR. CONCATO: Yeah, we're -- we're 19 going to break. But if I could just slip in for the 20 record --</p> <p>21 DR. GREENBERG: Yeah.</p> <p>22 DR. CONCATO: -- that Dr. Bo's</p>	<p>1 about various clinical trial design considerations. 2 And we've sort of broken it up into three distinct 3 topics acknowledging that these all sort of blur 4 together, and -- and it may just be one large 5 conversation here.</p> <p>6 But we wanted to focus on study 7 population, appropriate efficacy end points, and -- 8 and potential comparator treatment groups.</p> <p>9 And so we'll start again with the -- 10 with the ideal study population for clinical trial 11 enrollment, but again, sort of acknowledging that this 12 may all bleed together.</p> <p>13 So what thoughts do people have on sort 14 of what makes sense in the current landscape regarding 15 study design population, be it -- again, this is sort 16 of the old terminology, I guess, now. But symptomatic 17 versus isolated hearing loss versus asymptomatic or 18 some combination thereof.</p> <p>19 I can't see the -- this group is being 20 uncharacteristically quiet. Anybody want to take the 21 first step? Dr. Bo, go ahead.</p> <p>22 DR. BO: Maybe, actually, I'll break</p>

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<p>1 the ice a little bit.</p> <p>2 And, David, I -- I love that you raised</p> <p>3 your hand, because you've done a couple of landmark</p> <p>4 studies in -- in this area.</p> <p>5 And maybe I -- if I can frame the</p> <p>6 question in a way, maybe it -- it could help</p> <p>7 contribute a little bit further here on this question</p> <p>8 about the ideal study patient population and clinical</p> <p>9 trial enrollment in order to produce data that is</p> <p>10 going to be meaningful and essentially help to improve</p> <p>11 patient outcomes further, which is, based on your</p> <p>12 experience, David, with the two completed trials and I</p> <p>13 think a lot of what we've sort of discussed and</p> <p>14 learned throughout today.</p> <p>15 If you had to do it over again or -- or</p> <p>16 knowing what you know, what would you do differently</p> <p>17 around -- in order to -- to have the fastest and most</p> <p>18 effective way to produce data that could influence a</p> <p>19 practice among a patient population that has such dire</p> <p>20 needs, David?</p>	<p>1 And then the -- the safety issues came</p> <p>2 up. So that was the -- the reason for shutting down</p> <p>3 the trial.</p> <p>4 But what we found is that when a baby</p> <p>5 looks -- at least this is my interpretation of it,</p> <p>6 when the baby looks normal and you tell the parents</p> <p>7 who have never heard of CMV and they have this brand-</p> <p>8 new baby that the baby is infected, first of all, it</p> <p>9 takes a while to process that.</p> <p>10 And secondly, then you say, "Well,</p> <p>11 there -- and there's an 85 plus percent chance that</p> <p>12 she's -- the baby is going to be fine, and we want to</p> <p>13 give this drug for X number of months, are you</p> <p>14 interested in doing that?" And most of them said,</p> <p>15 "No, thank you."</p> <p>16 So -- so I think the asymptomatic</p> <p>17 population, unless we identify a way to enrich it with</p> <p>18 a biomarker that -- where we can -- we can be more</p> <p>19 assured that a particular baby is more likely to have</p> <p>20 hearing loss than just the general population of</p> <p>21 asymptomatic congenital CMV babies, I don't -- I don't</p> <p>22 see that as a population we can -- we can focus on.</p>
<p>21 DR. HODOWANECK: Excellent questions,</p> <p>22 Dr. Bo.</p>	Page 529
<p>1 Dr. Kimberlin?</p> <p>2 DR. KIMBERLIN: Well, that's a good</p> <p>3 question. I -- I don't know that I -- I don't know</p> <p>4 that the -- the basic study designs would have been</p> <p>5 different, even with -- with retrospective eyeglasses</p> <p>6 on.</p> <p>7 Certainly, the -- the follow-up would</p> <p>8 have -- we would have been much more diligent with the</p> <p>9 follow-up of the first study, the -- the IV</p> <p>10 ganciclovir versus no treatment randomized trial.</p> <p>11 That was our first real foray into the</p> <p>12 population and -- and it -- there are real challenges</p> <p>13 in studying congenital CMV.</p> <p>14 I think that for -- for -- well, I'll</p> <p>15 say -- I'll say this. One of the -- one of the things</p> <p>16 is asymptomatic. We tried to do an asymptomatic</p> <p>17 treatment study, and nobody wanted to be involved in</p> <p>18 it.</p> <p>19 It -- it -- we ended up having some</p> <p>20 toxicity issues as well. But the accrual was, to be</p> <p>21 honest -- it just wasn't -- it wasn't going to</p> <p>22 complete.</p>	<p>1 I think, you know, some -- hearing loss</p> <p>2 only, symptomatic, I mean, I -- I think we do have to</p> <p>3 keep in mind that the antivirals we've seen the data</p> <p>4 for, the antiviral drugs are -- valganciclovir is</p> <p>5 being used. I think we have to keep that in mind if</p> <p>6 we try to do a -- a placebo control in those</p> <p>7 populations. I don't think it would be -- I don't</p> <p>8 think anybody would sign up for it there either.</p> <p>9 I think for the next big advance, I</p> <p>10 would -- I would look toward combination antiviral</p> <p>11 therapy in populations already recommended to receive</p> <p>12 antiviral treatment.</p> <p>13 I would try to look at biomarker</p> <p>14 development. Although, you know, that -- that</p> <p>15 could -- we might have to wait five years to get those</p> <p>16 data, or they may never become available.</p> <p>17 So I'm not sure we should wait for</p> <p>18 that. But that's where I see things really -- really</p> <p>19 developing next, in my -- in my consideration.</p> <p>20 DR. VISWANATHAN: Thank you for those</p> <p>21 comments, Mr. Kimberlin. I have a quick -- and this</p> <p>22 is Prabha again. I have a quick follow-up question</p>

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1 for you. 2 You mention the difficulties with 3 accrual in the asymptomatic study. I'm curious 4 whether we -- we have a more -- a conversation that's 5 agnostic to the drug under study and then perhaps 6 there was one with a very clean safety profile, do you 7 think that -- that would be different? 8 DR. KIMBERLIN: So with -- so in other 9 words, with a different safety profile?	1 this would take a decade or two to do, but could we -- 2 could we have better education about CMV, so it's -- 3 they're not hearing about it two days after delivery 4 when the -- when the test comes back positive maybe. 5 But -- but again, that's not an 6 immediate fix for us, in terms of how do we move this 7 field forward now. 8 DR. HODOWANEC: Thank you, Dr. 9 Kimberlin.
10 DR. VISWANATHAN: A drug that perhaps 11 would need less laboratory monitoring, whether those 12 were factors, I guess, is my question. 13 Is -- is it the monitoring? Is it 14 simply the knowledge that probably your baby is going 15 to be fine and -- and that this -- nothing is needed 16 at all? I'm just curious if you could dig into that a 17 little bit more.	10 If we could shift just slightly back to 11 the isolated hearing loss population, you know, sort 12 of putting aside the issues of a comparator and 13 whether this would be an add-on to standard of care 14 study or those sorts of questions. 15 You know, I'm wondering if Dr. Schleiss 16 or anyone else would like to comment on sort of the 17 feasibility of enrolling that isolated hearing loss 18 population or challenges generally in that population, 19 given sort of the current variable screening 20 practices?
18 DR. KIMBERLIN: Yeah. I'm only 19 guessing. Because those that turned us down, we don't 20 collect data on, because they turned us down, and 21 we -- you know, we can't -- we can't do anything with 22 respect to -- to analyzing reasons, because they	21 DR. SCHLEISS: Yeah, I mean, I would 22 comment on -- on that in the context of Dr. Albert
1 didn't sign the consent form. 2 So my speculation though -- my 3 observation is that they just didn't -- they just 4 weren't interested. It -- it wasn't so much the 5 toxicity of the drug, it might have been the duration. 6 We -- we were proposing to treat for 7 four months. And that might have been off-putting. 8 So let's say you had a drug where you could give a 9 single shot, and it would -- IM injection, and it 10 would -- it would last -- it would do everything you 11 needed for it to do. That might be a different 12 matter. 13 But asking a family -- my experience 14 was asking a family who was -- who was just completely 15 blindsided by any of this, to -- to treat for at least 16 a longer period of time -- it wasn't so much the 17 toxicity of the drug -- I think for most of them, it 18 might have been for a few, but it was more just, "I 19 don't want to hear that. My baby is fine. Look at 20 him. Everything is good." And so I think that was 21 more what it was. 22 Now, could education of CMV -- again,	Page 531 1 Park's study throughout the University of Utah, a 2 really beautifully designed trial that was going to 3 try to -- to answer the question of whether isolated 4 sensorineural hearing loss is something that should be 5 treated with antiviral therapy, good controls, well 6 designed. 7 Enrollment was just impossible. It was 8 really difficult, and that study just simply couldn't 9 enroll enough babies to continue. So for some of the 10 reasons David brought up, I think future trials like 11 this are going to be really -- really very 12 challenging. 13 Now, with respect to, you know, the 14 universal screening, I -- I mean, that creates a whole 15 set of challenges in my mind, because all of -- all we 16 know, really, about antivirals in congenital CMV is 17 from babies that are identified in the context of 18 clinical care; right? 19 There's -- there's something about this 20 baby that prompts an -- an evaluation or workup, 21 whether it's a failed newborn hearing screen or some 22 other clinical finding, and now, we have all of these

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<p>1 babies who are -- are found by universal screening 2 where clinicians would not have thought to look. 3 And now, Megan Pesch has pointed out 4 quite eloquently in some of her writings and comments 5 that clinicians do overlook the obvious sometimes, and 6 that's another argument in favor of universal 7 screening -- babies that really should have been 8 picked up by a clinical acumen are -- are missed. 9 But let's face it, most of these babies 10 are asymptomatic. And so we do these evaluations. We 11 do these workups. And we find all of these incidental 12 findings that may or may not be important. 13 And -- and what -- what, indeed, do we 14 make of this finding of a -- of a subependymal cyst? 15 What do we make of this finding of leukostriate [sic] 16 vasculopathy? We pigeonhole these babies into 17 symptomatic categories. 18 But we need to recognize that all of 19 those categories were developed through workup and 20 evaluation and assessment of -- of babies who 21 identified in the course of clinical care as needing 22 an evaluation for congenital CMV.</p>	<p>1 hearing loss, and -- and that there is at least some 2 degree of symptomatology there, is there a role for 3 clinical trials for those patients? Is there a 4 timepoint beyond which we -- we don't think that 5 it's -- it's appropriate to be considering antiviral 6 therapies anymore. 7 Any thoughts on sort of these slightly 8 later diagnoses where we still think it's congenital 9 infection. But they're a little bit beyond the normal 10 window for when you would be considering starting 11 antiviral therapy under the current paradigm? 12 DR. KIMBERLIN: Well, I'll -- I'll jump 13 in. I hope Paul Griffiths can -- can follow with -- 14 with additional information. 15 But he alluded, I think, earlier to a 16 study that we did called the "Valgan Toddler" study, 17 and I think it was on one of the slides too. It was 18 published earlier this year in the Journal of 19 Pediatrics. 20 And -- and in that study, we enrolled 21 1-month to 4-year-of-age subjects. We intended for it 22 to be, overwhelmingly, exactly the population that you</p>
<p>1 So I guess I would argue we really need 2 very -- very rigorous studies of -- of these 3 asymptomatic babies identified by universal screening. 4 And -- and as I pointed out this 5 morning, I mean, maybe -- maybe the argument can be 6 made that newborn screening programs really shouldn't 7 be the focus of where these evaluations are being 8 done. Maybe they should be being done under the 9 leadership of any programs. 10 I don't know. But I -- I mean, I think 11 we're doing good. I think we're -- I think we're 12 helping babies by doing universal screening. But -- 13 but there are a lot of challenges, and it's -- it's 14 going to be really hard to sort -- sort these 15 asymptomatic babies out. 16 DR. PICA: Thank you. Thank you for 17 that, Dr. Schleiss. 18 I think to take this a step further, 19 well, what about, you know, the infants who were 20 asymptomatic at birth and then over, you know, the -- 21 the first several months of life are diagnosed, and -- 22 and you start to realize that they are having some</p>	<p>1 mentioned, somebody who -- who was normal at birth, 2 wasn't even tested for CMV most likely, developed 3 sensorineural hearing loss. 4 We go back and pull the -- they sign 5 informed consent; we go back and pull the dried blood 6 spot. They're PCR positive. Setting aside the 7 sensitivity of the dried blood spot, the specificity 8 would rule in congenital CMV, and then we randomize to 9 either six weeks of oral valgan or a placebo. 10 And we -- we enrolled -- took a while 11 to do it, because all these studies do, but we 12 enrolled the -- the study, and we saw no difference 13 whatsoever. Now, in retrospect, looking at the 14 population we actually enrolled, it was very 15 heterogenous. 16 It was -- we had -- we had more 17 symptomatics at delivery than asymptomatics at 18 delivery; that they had been treated initially, but -- 19 you know, so I -- I tend to think that probably is 20 either -- either it didn't work or we just -- our 21 population wasn't one that could have -- that could 22 determine whether it works.</p>

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<p>1 But nevertheless, it was -- it was a 2 negative study. Now, you contrast that with the -- 3 the CONCERT study from the Netherlands that was 4 mentioned, and what -- and that was really the basis 5 of the American Academy of Pediatrics Committee on 6 Infectious Disease's recommendation recently to -- to 7 treat isolated sensorineural hearing loss.</p> <p>8 And they did -- they -- theirs was not a 9 controlled study. But it -- but they did some really 10 nice statistical analysis, and they found a benefit.</p> <p>11 Now, in that study, they were very 12 rigid about not enrolling beyond 12 weeks, 6 days 13 following delivery. So up to 13 weeks is -- I think 14 Mark Schleiss mentioned in his talk. So I think 15 that -- and that's the reason, again, that the Red 16 Book Committee loosened up the time the drug could be 17 initiated -- started.</p> <p>18 But I think you'd have to say right 19 now, beyond 13 weeks -- 13 weeks, 0 days, the data, if 20 anything, would say it doesn't work. So, Paul, let's 21 here what you have to say about that.</p> <p>22 DR. GRIFFITHS: Well -- well, I agree,</p>	<p>1 that there would be lots of people who don't want to 2 go into trials. But the -- if you started national 3 screening in the whole United States, then there would 4 be enormous numbers coming through, and some parents 5 might want some action taken, as long as at the time 6 you ask them, "Are you prepared to be randomized to 7 drug versus placebo?" And if they say, "Yes," then 8 they could be recruited at that particular time.</p> <p>9 DR. PICA: Thank you, Dr. Griffiths.</p> <p>10 Anyone else have any thoughts regarding population 11 that they would like to share, any follow-up 12 questions?</p> <p>13 All right. Then let's move on to talk 14 about end points. And again, we've sort of already 15 started down this discussion path. And, you know, we 16 talked a lot about various hearing related end points.</p> <p>17 But we've also heard that -- that might not be the 18 most meaningful end point to -- to patients and 19 parents.</p> <p>20 So I -- I'd love to hear the -- the 21 panel's thoughts on that, hearing versus other longer 22 term, other neurodevelopmental outcomes, from both a</p>
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<p>1 David, with that analysis. And I just wonder if we 2 should tie this in with Dr. Pesch's talk -- her second 3 talk where she argued that perhaps we should move away 4 from this classification of -- into symptomatics and 5 asymptomatics.</p> <p>6 Perhaps we should have randomized 7 controlled trials designed to recruit patients who 8 present in certain ways to the medical system.</p> <p>9 So those who were born in a hospital 10 and have symptoms and are worked up and found to have 11 congenital CMV that can be called "symptomatics," and 12 that's kind of the same as normal.</p> <p>13 But those who don't have a clear signal 14 on their hearing screening test are probably a 15 different group. They're all in the first few weeks 16 of life, and then perhaps reasonably, homogeneous.</p> <p>17 The other ones who present, they're 18 quite -- quite different; aren't they? Perhaps they 19 should be recruited into a different study. Perhaps 20 they should be on means of presentation that leads you 21 to have a classification.</p> <p>22 And as for the asymptomatics, I accept</p>	<p>1 meaningfulness perspective and then also balancing 2 that with a feasibility perspective.</p> <p>3 I know we've heard a lot about how 4 challenging these long follow-up periods are to 5 implement. So I'd like to hear the panel's thoughts 6 on -- on these potential clinical end points.</p> <p>7 Dr. Pesch, please go ahead.</p> <p>8 DR. PESCH: Thanks. I'm -- I'm driving 9 my daughter home from school right now. This is -- so 10 I hope my audio is okay.</p> <p>11 You know, as much as I said that I 12 don't think hearing loss is the most important thing 13 to families. It is a relatively clean outcome to 14 measure and present relatively early.</p> <p>15 I especially appreciate Dr. Kimberlin's 16 point about the five-year grant cycle and how quickly 17 you kind of need that data.</p> <p>18 So many more of these perhaps nuanced 19 developmental outcomes, you know, may require a decade 20 to -- to measure, and I would also say are a lot more 21 expensive to measure longitudinally than, you know, 22 hearing in the neonatal period. So it -- it is</p>

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<p>1 tricky.</p> <p>2 DR. HODOWANEC: Thank you, Dr. Pesch.</p> <p>3 Yes. I mean, it seems that perhaps measuring hearing</p> <p>4 in the short-term, but continuing to follow these</p> <p>5 patients, if possible, to get those longer term</p> <p>6 outcomes would be really the ideal path, I think.</p> <p>7 Sticking with the hearing-related end</p> <p>8 points, I -- I'd be curious to see what -- what people</p> <p>9 think, you know -- particularly, hearing more from</p> <p>10 our -- from our audiology and -- and ENT analysts,</p> <p>11 if they have additional comments on this.</p> <p>12 But sort of what -- what makes the most</p> <p>13 sense to look at here in terms of best ear, worst ear,</p> <p>14 total ear? It seems, like, depending on which of</p> <p>15 those you choose, you -- you could have very different</p> <p>16 results.</p> <p>17 And -- and so how do we -- you know,</p> <p>18 as -- as I think Dr. DeVries had outlined, there's</p> <p>19 sort of pros and cons to each of those approaches to</p> <p>20 measuring hearing. But -- but how do we move forward</p> <p>21 with potentially designing a clinical trial and</p> <p>22 selecting a primary end point in a timepoint in which</p>	<p>1 rare diseases, we need a primary end point, because</p> <p>2 you got to have a primary end point.</p> <p>3 But -- but things shouldn't be judged</p> <p>4 just on the primary end point. We should be looking</p> <p>5 at the full story that's being told across a given</p> <p>6 study and across multiple studies to see what the</p> <p>7 totality of the indication is with respect to whether</p> <p>8 it works or not.</p> <p>9 And it's not perfectly clean. It's not</p> <p>10 as pristine as -- as, you know, enrolling 50,000</p> <p>11 people and hitting your primary end point. I</p> <p>12 understand that.</p> <p>13 But I think it's the reality of these</p> <p>14 rare disease, at least rare infectious disease,</p> <p>15 situations that we're -- we're trying to have -- move</p> <p>16 the needle on and make things better.</p> <p>17 DR. HODOWANEC: Thank you, Dr.</p> <p>18 Kimberlin. We -- we hear you, and -- and we do, you</p> <p>19 know -- we definitely support the idea of looking at</p> <p>20 the -- the totality of the data. But we do also need,</p> <p>21 you know, persuasive data at the end of the day.</p> <p>22 I will now call on Dr. Griffiths.</p>
<p>1 that primary end point is -- Dr. Kimberlin?</p> <p>2 DR. KIMBERLIN: Well, the -- the</p> <p>3 benefit of total ear is -- is it doubles your sample</p> <p>4 size in terms of the numbers of people enrolled,</p> <p>5 because everybody has two ears. And -- and given</p> <p>6 the -- the challenges with these studies, that, I</p> <p>7 think, can be helpful. So -- so that -- that would be</p> <p>8 point number 1.</p> <p>9 And then trying -- I think trying to</p> <p>10 protect hearing -- now, that's not to say -- you know,</p> <p>11 protecting normal hearing would be great and should be</p> <p>12 part of it. But also protecting, you know, if you</p> <p>13 have moderate hearing loss and -- and that gets</p> <p>14 protected, that's good too, or at least it's</p> <p>15 meaningful as well.</p> <p>16 So I think -- I think protecting what</p> <p>17 you got, rather than seeking to improve, is probably</p> <p>18 more realistic with -- at least with the drugs and the</p> <p>19 understanding of the disease that we have right now.</p> <p>20 And then I would -- I would come back</p> <p>21 to a point I tried to make rather inarticulately</p> <p>22 yesterday, I think. I -- I really think for these</p>	<p>1 DR. GRIFFITHS: So looking at your</p> <p>2 request to focus on real-world data, could we have</p> <p>3 primary end points as did the child need a hearing</p> <p>4 aid; did the child need cochlear implants; did they</p> <p>5 need to have special arrangements for their schooling</p> <p>6 because of their hearing problem?</p> <p>7 Could those be worked up into a</p> <p>8 composite, so perhaps those who didn't need any of</p> <p>9 those interventions versus those who needed one of</p> <p>10 them? Because of course, they may overlap, and they</p> <p>11 have more than -- more than one.</p> <p>12 Should we be trying to look for real-</p> <p>13 world data that -- that makes sense to patients and</p> <p>14 their parents?</p> <p>15 DR. HODOWANEC: I see that Dr. Pesch</p> <p>16 had her hand raised, and I will come to you in one</p> <p>17 moment. But I also -- I'm first going to turn to Dr.</p> <p>18 John Concato who may have some comments on -- on the</p> <p>19 feasibility of using real-world evidence for -- for</p> <p>20 those type of data collection, those types of end</p> <p>21 points.</p> <p>22 DR. CONCATO: Yeah. Just as there were</p>

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<p>1 issues this morning of terminology for CMV itself, I 2 think there's issues in terminology of real-world data 3 -- and it's nothing -- no one said anything wrong. 4 But what I heard actually, we're still 5 talking about a traditional randomized trial. We're 6 just talking about changing the outcome, the end 7 point, and we've looked for something that tells us 8 how the patient feels, functions, or survives. 9 So I don't have a problem, 10 quote/unquote, "wearing my real-world evidence hat," 11 or "real-world data." I'm talking about -- I think 12 we're still on part of the landscape where we're 13 talking about doing a clinical trial. 14 So I would probably go back to the 15 division and say, you know, "What's your thinking?" 16 We're not talking about any drug right now. But -- so 17 I think when I -- I hear "real-world data," "real- 18 world evidence," I -- I pause to ask what the source 19 of data would be and what the study design would be if 20 it's -- if that's helpful. 21 Thank you. 22 DR. HODOWANEC: Thank you, Dr. Concato.</p>	<p>1 that's kind of the lower threshold, unilateral. 2 There's somewhat less of an urgency. 3 So maybe closer to 12 months this -- 4 you know, it's gone down even since my daughter had 5 her cochlear implants, which was not too long ago, so 6 previously 12 months. So I -- I -- does that answer 7 the first question? 8 DR. HODOWANEC: Yes. Thank you. 9 That's very interesting -- appreciated how early that 10 can be. 11 DR. PESCH: Yeah. And I guess the 12 other -- the point I -- I just wanted to make is kind 13 of just to embellish off a point that Dr. Griffiths 14 and Dr. Kimberlin made was that even -- so looking at 15 hearing loss progression, but also the timing of that 16 progression, every month that hearing -- prelingual 17 access to sound can be preserved -- even if the end 18 point is profound hearing loss, if that profound 19 hearing loss occurs when the child is 18 months versus 20 6 months, the difference in terms of cognitive develop 21 and language develop -- development, assuming, you 22 know, that child has hearing parents and the child,</p>
<p>1 And if I could just follow up on Dr. Griffiths' 2 question, you know, I -- I think that the idea of a 3 composite end point, like you proposed, I think that 4 that's -- I think that's an interesting idea that -- 5 that we certainly should consider. 6 I'm curious from the clinicians, what 7 is the timeframe typically -- and I'm sure this is 8 variable, but for -- for those children who have 9 congenital CMV infection? What is the typical 10 timeframe with which a cochlear implant might be 11 needed? 12 UNIDENTIFIED SPEAKER: And is there 13 even consistency -- 14 DR. PESCH: I can answer -- 15 DR. HODOWANEC: Oh, thank you. Sorry. 16 Thank you. Yes, please, Dr. Pesch. 17 DR. PESCH: Yeah, I can answer that. 18 So at least in the U.S., if it's congenital, like, 19 from birth, hearing loss in a severe to profound 20 range, nine months is when -- right now, cochlear 21 implants are occurring. 22 Although, for bilateral, I should say,</p>	<p>1 you know, likely doesn't have access to sign language 2 is -- is -- it's really -- it can really make a huge 3 difference. 4 So not only the end points, but also 5 kind of the trajectory of that, how -- the -- the 6 decrease in the hearing loss progression. 7 DR. HODOWANEC: Thank you, very much, 8 Dr. Pesch. Appreciate those perspectives. We have a 9 comment in the QR -- I guess a question in the Q&A 10 from Dr. Shannon Ross. 11 "Could anyone comment on vestibular 12 dysfunction? There's increasing data that this 13 affects children with congenital CMV with and without 14 hearing loss and can impact motor development." 15 I don't know if Dr. Pesch or anyone 16 else has any insight on that -- that they would like 17 to share. 18 DR. PESCH: Sure, I can address that. 19 Yeah, absolutely, and we're seeing it in children -- 20 and, like you said, Dr. Ross, without hearing loss as 21 well. 22 In my clinical experience, I almost see</p>

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<p>1 it always go hand in hand with hearing loss, and I 2 think that is a big part of the gross motor delays, 3 like the softer gross motor delays that we see in 4 these kids, because they -- you know, as toddlers, the 5 world goes "whoosh" when they move their heads, and so 6 it's that fear almost of taking steps.</p> <p>7 I think we're learning more and more 8 about the potential of vestibular rehab in that 9 optimal window between 4 and 8 years of age.</p> <p>10 I think there is a study going on now, 11 a multi-institutional collaboration, looking at some 12 more data from these kids with CMV and pre- and post- 13 cochlear implant, because that's another thing that 14 might impact vestibular function. So I think it's a 15 really hot area and more to be learned soon.</p> <p>16 DR. HODOWANEC: Thank you, so much, 17 for -- for sharing all those perspectives, Dr. Pesch, 18 and I -- I have another follow-up for you. But for 19 anybody else who -- who wants to take this.</p> <p>20 So I'm -- I'm hearing you say the 21 maintenance of hearing -- the preservation of hearing 22 through that sensitive period of -- of speech and</p>	<p>1 can be a functional measure -- or functional form of 2 language and communication for a child, so -- which 3 is, of course, different than -- than measuring, you 4 know, the hearing loss.</p> <p>5 So I think -- I don't really know if 6 you can say one is more important than the other. I 7 think it would be good to measure all communication in 8 language, because we do -- are seeing more multi-modal 9 communications from these kiddos that can be somewhat 10 functional. So I -- I'm going to -- I'm going to play 11 for both teams and say both.</p> <p>12 DR. HODOWANEC: Fair enough. They -- 13 they both sound, like, they could be meaningful end 14 points. And you're not at all hogging the discussion 15 here. We -- we very much appreciate the sort of 16 unique perspective that you bring to this discussion, 17 and we certainly, obviously, welcome others to chime 18 in as well.</p> <p>19 But while we have you, Dr. Pesch, one 20 other follow-up question we had, so if in some of the 21 parent groups that you're part of -- trying to get a 22 sense of sort of how the excused or what the</p>
<p>1 language development is critical. I think I heard the 2 same from Dr. Kimberlin.</p> <p>3 So perhaps, I mean, in my mind, I'm 4 envisioning sort of a flat audiogram that doesn't 5 change or doesn't deteriorate over time. Is the end 6 point then that we'd be looking at really that 7 audiogram and the preservation of hearing, or is it 8 really what comes as the consequences of that?</p> <p>9 Is it the speech and language 10 acquisition? Is it other developmental milestones? 11 And I know these are -- these are challenging end 12 points to measure. But I just would like to hear your 13 thoughts about that.</p> <p>14 DR. PESCH: I feel, like, I'm hogging 15 the show here -- hogging the spotlight. I'll just say 16 really quickly, they're kind of, you know, two 17 separate things, I think, you know, language and 18 communication measured functionally.</p> <p>19 You know, if a child has access to, you 20 know, sign language, I know it's -- it's very 21 different than spoken language in terms of -- except, 22 like, how widely spread and available it is, but that</p>	<p>1 proportions are for those who have maybe more, you 2 know, just isolated hearing loss versus more 3 symptomatic cases of congenital CMV infection, is it a 4 pretty even mix?</p> <p>5 Could you just tell us a little bit 6 about sort of the -- the makeup of -- of the groups 7 that -- that you work with?</p> <p>8 DR. PESCH: Yeah. Yeah, absolutely.</p> <p>9 So I tend to see probably a pretty even distribution 10 in terms of who we would think would be getting 11 diagnosed, you know, because knowing that children 12 with symptomatic CMV in the absence of a screening 13 program would be getting diagnosed more often.</p> <p>14 So I'd say it's probably, like, a 50/50 15 split early on, so in the infancy period. But then 16 the families with kids who have unilateral hearing 17 loss or isolated hearing loss, I think they tend to 18 make their way to other groups.</p> <p>19 Like, there's some really robust parent 20 support groups for children with hearing loss. And 21 it's the families with the kids who are either more 22 symptomatic or, like, thought were asymptomatic at</p>

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<p>1 birth, but perhaps have some evolving behavioral 2 difficulties, those are the ones that really stick 3 around.</p> <p>4 And we see the posts from older -- 5 parents of older kids are primarily from this -- this 6 symptomatic group.</p> <p>7 DR. HODOWANEC: Thank you, Dr. Pesch.</p> <p>8 Roberta, we're wondering -- sorry. Dr. 9 DeBiasi, we're wondering if -- if you would like to 10 share sort of your perspectives based on your patient 11 panel, you know, what -- what you think would be 12 meaningful to your patients in terms of some of these 13 various end points that we've talked about.</p> <p>14 I'd be curious also to hear your 15 thoughts on -- on the composite end point or example 16 of a composite end point that Dr. Griffiths put out.</p> <p>17 DR. DEBIASI: Yeah. I mean, I -- I 18 concur with Dr. Pesch that the hearing is important to 19 evaluate, but is not the primary thing that our 20 patients are worried about.</p> <p>21 They are really worried about the MRI, 22 the findings, and the cysts, and the white matter</p>	<p>1 terminology, then -- then yes, I think they're going 2 to be more worried about it.</p> <p>3 If it's somebody that failed their 4 newborn hearing screen and they're just learning about 5 CMV for the first time as they get tested and -- and 6 then follow-up, they're going to be worried about 7 hearing.</p> <p>8 So I -- I think it depends on -- on 9 what subset of the population we're talking about, and 10 I think you got to recognize that the larger subset is 11 going to have isolated hearing loss.</p> <p>12 So -- so they're going to be less -- 13 less severely affected at the outset than -- than the 14 population that -- that would have -- be more likely 15 to have neurologic sequelae as a consequence.</p> <p>16 So longwinded way to say, I -- I follow 17 what's being said; I'm not sure I would say that's 18 been my experience.</p> <p>19 DR. DEBIASI: I just -- just to 20 embellish on what I -- I mean, you know, the kids that 21 are severely affected and have microcephaly and 22 polymicrogyria, you know, that's a matter of</p>
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<p>1 changes, and what does that mean, and is their child 2 going to be able to go to school normally, and, you 3 know, those sort of things.</p> <p>4 So if we could become more focused on 5 some of those end points using more quantitative 6 correlates of that, I think that would be useful. So, 7 you know, those would be my general thoughts.</p> <p>8 Of course, the hearing is extremely 9 important. But I really do think if we focus only on 10 that or mostly on that, we're not really focusing on 11 what families are worried about.</p> <p>12 DR. HODOWANEC: Thank you, Dr. DeBiasi.</p> <p>13 And, Dr. Kimberlin, do you have a similar experience 14 with your -- your patients or anything different to -- 15 to note?</p> <p>16 DR. KIMBERLIN: I don't know that I 17 would have the same experience. I mean, certainly, 18 neurologic is important. But I think it depends 19 on -- on sort of who you're having the conversation 20 with.</p> <p>21 If it's a child who is microcephalic 22 and -- and overtly symptomatic to use that</p>	<p>1 explaining to the family that those things are 2 unlikely to be reversible and have a bad outcome.</p> <p>3 But it's all these other middle of the 4 road things that I think people really -- we don't 5 know what to tell them. They're very worried about 6 it.</p> <p>7 And that can still include, "What does 8 that mean for hearing?" But maybe better ways to 9 follow these changes serially and correlate them with 10 other things, like these biomarkers that you're 11 talking about. I think that would be helpful.</p> <p>12 DR. PICA: Thank you, Dr. DeBiasi. Any 13 additional thoughts or comments regarding end points 14 before we move on to the final topic?</p> <p>15 Okay. With that, I will move on to -- 16 to I think one of -- not that they're not all 17 challenging, but one of the most challenging, I think, 18 discussion points is -- is regarding trial design 19 and -- and use of a comparator.</p> <p>20 And I think, you know, we've heard loud 21 and clear today that in the hearing loss population 22 and the symptomatic population, that placebo</p>

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<p>1 controlled trials are likely not to be feasible.</p> <p>2 And so let's talk about other potential</p> <p>3 approaches in -- in those populations, in terms of an</p> <p>4 add-on to standard of care type of trial design.</p> <p>5 What -- what do people think is -- is a</p> <p>6 feasible way for potentially studying new therapies,</p> <p>7 given the current landscape?</p> <p>8 DR. HODOWANEC: Go ahead, Dr. DeBiasi.</p> <p>9 DR. DEBIASI: This may not be answering</p> <p>10 the question, or maybe I misunderstood the question.</p> <p>11 But, you know, it would be hard to not use valgan,</p> <p>12 since we have such great data that it has an effect.</p> <p>13 So to me, anything we would do at this</p> <p>14 point would have to be adjunctive therapy, like is</p> <p>15 being done with the CPIC trial right now.</p> <p>16 But I don't know. I'm interested to</p> <p>17 hear other people's thoughts about that. So to me, it</p> <p>18 would be most interesting to use things that we know</p> <p>19 work, plus and minus other things that we want to know</p> <p>20 if they improve -- what we already have seen for</p> <p>21 improvement.</p> <p>22 DR. VISWANATHAN: Thank you for that,</p>	<p>1 DR. DEBIASI: Well, I think clear is</p> <p>2 hard for this whole area. I mean, obviously, nothing</p> <p>3 is clear. But if we're going to continue to focus on</p> <p>4 the hearing loss, it makes sense to me that we build</p> <p>5 on what we already have, like is being done. But the</p> <p>6 idea is, are there other things that could be looked</p> <p>7 at, besides letermovir.</p> <p>8 Should we be using adjunctive anti-</p> <p>9 inflammatory therapies as another choice, or should</p> <p>10 you be using some other antiviral in addition to</p> <p>11 valgan? But that would be my thought.</p> <p>12 DR. GREENBERG: I think the challenge</p> <p>13 for new drug development -- and, you know, others can</p> <p>14 please feel free to weigh in, but, you know, if your</p> <p>15 comparator is -- is valgan, you know, you might -- if</p> <p>16 you -- if you propose to have a safer therapy than --</p> <p>17 than valgan, then you have to do -- you still have to</p> <p>18 have a superiority trial.</p> <p>19 You can't win with a noninferiority</p> <p>20 trial in a safer medication, because valgan, in the</p> <p>21 eyes of the -- right in the eyes of the regulatory</p> <p>22 authority is not, you know, indicated for this</p>
<p>1 Dr. DeBiasi. And so what I'm hearing there is -- so</p> <p>2 there is -- they're studying valganciclovir, plus or</p> <p>3 minus adjunctive therapies.</p> <p>4 What if it was a novel antiviral?</p> <p>5 How -- how would you see that being incorporated into</p> <p>6 the -- into the clinical trial design?</p> <p>7 DR. DEBIASI: Well, I think it would be</p> <p>8 hard for me to enroll people if you mean only the</p> <p>9 novel antiviral versus something that we've already</p> <p>10 studied and know has an effect. So that -- that would</p> <p>11 be my point.</p> <p>12 DR. VISWANATHAN: We recognize also</p> <p>13 that the -- the answer to this question depends on the</p> <p>14 population under study and -- and those -- the certain</p> <p>15 population where there might be more equipoise about</p> <p>16 whether antivirals are affected.</p> <p>17 We would love to hear your thoughts in</p> <p>18 any population -- if -- if there's any clarity in</p> <p>19 anyone's mind about a population in which it would be</p> <p>20 clear what the design would be.</p> <p>21 The silence is very informative,</p> <p>22 indeed.</p>	<p>1 population.</p> <p>2 So I think, you know, it becomes a real</p> <p>3 challenge for developing new things, even if you try</p> <p>4 to use valgan as a comparator.</p> <p>5 DR. HODOWANEC: Does anyone have any</p> <p>6 comments on duration of therapy and -- and sort of how</p> <p>7 competent people are that -- that six months is -- is</p> <p>8 the right duration -- optimal duration?</p> <p>9 I don't know if -- you know, I think it</p> <p>10 depends on the -- the type of therapy. But, you</p> <p>11 know, for -- for antivirals in particular, how</p> <p>12 confident are we that six months is enough?</p> <p>13 Would there be different outcomes if we</p> <p>14 studied -- continued an antiviral therapy for -- for a</p> <p>15 longer duration or if we had, you know, a more -- a</p> <p>16 drug that could be tolerated and potentially</p> <p>17 administered for longer, given that, you know, we've</p> <p>18 heard that these hearing outcomes are really evolving</p> <p>19 over many years, not just the first six months or --</p> <p>20 or so of life.</p> <p>21 Well, I'm sure David has thought about</p> <p>22 this a lot. We're waiting to hear what he would say</p>

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<p>1 about it. But I can just tell you, the families are 2 very happy to stop at six months. They are marking it 3 on their calendar and very happy when it's over. 4 So, you know, selling it for longer I 5 think will be harder. But -- but there's certainly 6 reasons why if you follow the logic of the studies 7 that have been done so far, why treating longer would 8 be maybe a good idea, if it's ongoing viral that -- 9 that we're looking for, which we just said we don't 10 know. So that's the tricky part.</p>	<p>1 DR. PICA: Thank you, Dr. Schleiss. I 2 know there's been a lot of interest in looking at the 3 T-cell -- you know, CMV-specific T-cell responses in 4 the transplant setting and -- and sort of along those 5 same lines, thinking that long periods of -- of drug 6 exposure of prophylaxis could ultimately just sort of 7 delay the -- the natural immune response and could 8 have some potential negative impacts. 9 But yes, I think it seems, like, 10 there's a lot unknown about that in the congenital CMV 11 space. But that's a great point.</p>
<p>11 DR. KIMBERLIN: Yeah, I think I -- I've 12 had the same experience where -- where they're happy 13 when they get to the -- the finish line of six months.</p>	<p>12 Dr. Kimberlin? 13 DR. KIMBERLIN: A couple of points.</p>
<p>14 I'll say that we could entertain a 15 three-year-treatment course. We can't get it funded 16 to study it, because there's not enough time to treat 17 for -- to write the protocol to treat for three years 18 and to follow to know.</p>	<p>14 Mitch Cairo has a study that's starting soon using 15 CTLs in congenital CMV up in New York, and so that's 16 one to keep an eye on. And -- boy, that was -- so 17 that popped in my head, and I blanked on what else I 18 was going to -- oh, I know what it was.</p>
<p>19 So to some extent, we can hypothesize 20 all we want. We're going to run up -- at least I 21 believe we're going to run up against the reality of 22 what can get done.</p>	<p>19 The idea of -- the talk earlier about 20 different ways to administer a drug was interesting to 21 me. You know, ocular ganciclovir implants -- I looked 22 it up during the talk, because I didn't know how big</p>
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<p>1 DR. SCHLEISS: Yeah, I -- I mean, every 2 family is different. I -- I agree with Roberta. Most 3 families are quite happy to reach the finish line.</p>	<p>1 they were, they're 4 millimeters in diameter.</p>
<p>4 But I've had a few families that want 5 to go longer. I've had, you know, some families tell 6 me that -- in various chatrooms and Facebook groups, 7 that they know some clinicians who are treating for a 8 year, and that -- that makes me nervous without any 9 data to support it.</p>	<p>2 I have no idea how much space there is 3 in the middle ear of a -- of an infant. But -- but 4 could a -- could an implant delivering drug locally, 5 assuming it crosses into the inner ear, could that be 6 a way to have sort of a one-time intervention with a 7 longer duration of potential treatment effect? I 8 don't know.</p>
<p>10 But it just kind of underscores that, 11 you know, there's a wide range of opinion about 12 everything on the internet, I suppose.</p>	<p>9 DR. HODOWANEC: Thank you, Dr. 10 Kimberlin. We -- we were -- we were similarly 11 intrigued by this possibility of -- of a more local 12 administration and whether there could be some sort of 13 extended release at -- at the site of -- of concern.</p>
<p>13 It gets back to what I was talking 14 about a little bit earlier too in terms of the longer 15 you suppress replication, the less likely you will to 16 develop a protective T-cell response, perhaps.</p>	<p>14 I don't know if -- if Dr. Kau is on 15 the -- on the call. If have -- you have any 16 additional comments, we'd love to hear.</p>
<p>17 And I still think that that's something 18 we need to look at in terms of the impact of long 19 courses of antivirals on eventual T-cell control. 20 Although, the -- the paper from the Spanish group that 21 I referenced earlier suggests that -- that doesn't 22 seem to correlate with sequelae.</p>	<p>17 DR. KAU: Yeah. I think -- 18 DR. HODOWANEC: Go ahead. 19 DR. KAU: Oh, sorry. 20 DR. HODOWANEC: Go ahead. 21 DR. KAU: I think the idea of 22 putting -- that's an interesting idea. I don't -- I</p>

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<p>1 don't -- you know, there is issues with anything going 2 into the middle ear, because that in and of itself can 3 cause some conductive loss just by being there.</p> <p>4 You know, I probably don't know the 5 exact size of a neonate, but -- middle ear space, but 6 it's interesting. I think if you could find a way to 7 do something like that where it wouldn't interfere, 8 perhaps you can get some exposure to round window. 9 But I would -- I would think it would have to be quite 10 small.</p> <p>11 DR. KIMBERLIN: Yeah, I -- I would just 12 point out that Dan -- I helped Dan Choo at Cincinnati 13 Children's write an RO1 some years ago, which we 14 looked at -- at a preclinical model in guinea pigs to 15 ask this very question, inspired, in part, by some of 16 the interocular ganciclovir data that goes all the way 17 back to the pre-heart -- the therapy era and HIV 18 patients.</p> <p>19 There was a time in the, you know, late 20 '80s, early '90s that interocular ganciclovir was -- 21 was not, you know -- was -- was used actually fairly 22 often.</p>	<p>1 I don't know if -- if that's been 2 looked at in that model or not -- antivirals. I don't 3 know if Emma is still on the -- on the call. She -- 4 she might -- might know that literature.</p> <p>5 But it's a great idea. Would be great 6 to see some local delivery techniques for CMV inner- 7 ear disease.</p> <p>8 DR. HODOWANEK: Yeah. Thank you for 9 all of those comments. I wanted to acknowledge Dr. 10 Abzug's comment as well that this is given that the -- 11 the drug itself would not be cytotoxic in and of 12 itself if administered through this route.</p> <p>13 But we did think it was kind of a 14 provocative idea, especially for those children where 15 that duration of therapy is not really well known. We 16 know that there's both pragmatic challenges to 17 prolonged systemic therapy, as well as the side 18 effects of -- of that exposure.</p> <p>19 And so if you have a child, a toddler 20 perhaps, with tympanostomy tubes, you could inject via 21 that tube for local therapy. Something just -- food 22 for thought.</p>
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<p>1 And there was another drug, fomivirsen, 2 that was approved for intraocular inoculation for HIV- 3 infected patients with CMV retinitis. I don't think 4 that's on the market anymore.</p> <p>5 But anyway, Dan and I tried to pilot 6 this in guinea pigs. Part of the problem was that the 7 guinea pigs' cytomegalovirus is intrinsically 8 resistant to ganciclovir, so we could never really do 9 efficacy studies in the animal model.</p> <p>10 But I was glad to hear that talk 11 earlier today, because it is something I know Dan is 12 still interested in at Cincinnati. And that would -- 13 I mean, wouldn't that be great if you had a long- 14 lasting antiviral implant, and it actually worked, and 15 you could avoid the systemic toxicities of 16 ganciclovir?</p> <p>17 So I think intratympanic injection -- 18 not a new idea, but one that we certainly need to 19 continue to think about, and maybe we can find a way 20 to dust off the guinea pig model and find -- find some 21 other strategy or some other antiviral to revisit that 22 question or even the rhesus macaque model.</p>	<p>1 And, Dr. Griffiths, I see that you have 2 a comment to make.</p> <p>3 DR. GRIFFITHS: Yes, I was just going 4 to get back to the question -- somebody said, "Does 5 the antiviral drug suppress immune responses?" And 6 there's evidence from a solid organ transplant in a 7 randomized controlled trial, seronegative individuals 8 randomized to valganciclovir prophylaxis or 9 ganciclovir given preemptively.</p> <p>10 And preemptive was superior to 11 prophylaxis in terms of preventing late onset disease. 12 And they published a paper recently showing an 13 explanation for this.</p> <p>14 There's blood -- or blunted CD4, CD8, 15 and antibody responses in those who receive the drug 16 continuously, rather than intermittently and presuming 17 the drug is potent enough to delay antigen 18 presentation to the immune system.</p> <p>19 That's about the only evidence I know. 20 We have to be a bit care -- a bit careful before 21 applying this to -- to children.</p> <p>22 Of course, we're talking about neonates</p>

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<p>1 here that have immature immune responses. But they're 2 not receiving immunosuppressant drugs. But they have 3 had long antigen exposure in utero before they come to 4 your attention. So there are quite a few differences 5 between the two groups.</p> <p>6 DR. PICA: Thank you, Dr. -- Dr. 7 Griffiths. Excellent points. Any other comments on 8 the comparator topic or any other trial design 9 comments before we move into our -- our last 10 discussion point here, which is sort of the sub bullet 11 of -- of the comparator discussion looking into real- 12 world evidence.</p> <p>13 Okay. So I mean, we've sort of already 14 been -- been somewhat dancing around this issue of 15 what is the -- the rule for utilizing or leveraging 16 real-world evidence to help advance drug development 17 in the congenital CMV space, given all of these 18 clinical trial pragmatic challenges?</p> <p>19 We want to just open the floor for any 20 additional thoughts -- comments that people might have 21 on how you see real-world evidence potentially playing 22 a role. And I will let Dr. John Concato start.</p>	<p>1 design types? 2 Because I think it's -- there's so many 3 moving parts. We need to be clear where exactly we 4 are on that so-called "landscape." Does that make 5 sense, Aimee?</p> <p>6 DR. HODOWANEK: Thank you, Dr. Concato. 7 Yes, it does make sense. And -- and I think we didn't 8 necessarily have a specific potential approach to the 9 utilization of real-world evidence in the congenital 10 CMV space. I think we wanted to just sort of get 11 the -- the group's thinking on this.</p> <p>12 DR. CONCATO: And I'll just make one 13 more point. I mean, it's a tie-back to what was 14 mentioned earlier, and credit to Dr. Abzug for 15 bringing it up. If we go back to the specific 16 question, this is not about getting a new drug 17 approved.</p> <p>18 But if there's concern about 19 carcinogenicity, I stand by what I said earlier, it's 20 not easy. On the other hand, you know, we shouldn't 21 give up on it.</p> <p>22 So if we're looking to see whether a,</p>
<p>1 DR. CONCATO: Yes. I'll admit to not 2 answering your question, but rather, hopefully, 3 enabling a discussion by describing briefly what might 4 be the landscape, at least from one perspective.</p> <p>5 Do we agree if we have a new molecular 6 entity, you know, by definition, we don't have real- 7 world data available? So in that case, we will think 8 of our faced approach to trials, and we could talk 9 about what exact, you know, trial needs to be 10 designed.</p> <p>11 And a second layer, there are improved 12 drugs, say, for CMV in adults. And this is where we 13 heard this morning from Dr. Greenberg about the PTN 14 and how -- but that would depend on doing another 15 trial as well.</p> <p>16 So if we have approved drugs where 17 "real-world data," quote/unquote, are available, but 18 we're thinking about more -- that more generally, 19 that's where I think the question -- that's where I 20 might toss it back to you, Aimee, is that -- is that 21 what you're asking about, specifically, whether we're 22 talking about externally controlled trials or other</p>	<p>1 quote/unquote, "signal" is there, that's where I'm 2 certainly not speaking on behalf of the Critical Path 3 Institute. But I will connect the dots between 4 today's discussion and yesterday's for those who 5 missed yesterday's.</p> <p>6 One of the projects that the FDA is 7 supporting is with the International Neonatal 8 Consortium. Their -- the focus of the award was to 9 look at lab values, and they have a -- they were 10 working on a disease model for bronchopulmonary 11 dysplasia. So it's not CMV, and again, I'm not a 12 pediatrician or a neonatologist.</p> <p>13 I'm not speaking for C-Path. But with 14 400,000 plus -- with the data on more than 400,000 15 plus neonates, I -- our one question might be whether 16 it's worth giving those folks a call to see what they 17 have and whether it -- it's a future grant, even if 18 it's looking at the natural history, et cetera, or 19 looking for a signal back to the -- the question of 20 whether or not cancer is increased or not.</p> <p>21 I know this is a somewhat of a diffused 22 comment. But I'm just trying to help by seeing where</p>

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<p>1 we might put down a stake in the ground and -- and 2 have some -- some anchor to start with.</p> <p>3 So both a general comment about the 4 landscape, as well as the specific comment about, I 5 think -- yeah, that if the data are -- if -- if the 6 signal is out there, we should be able to find it.</p> <p>7 And one -- one last point, sorry for 8 bouncing around, but I -- I would ask Dr. Greenberg to 9 comment on PSNet. I know they're not always doing 10 trials. But we have a separate -- one more vignette.</p> <p>11 The FDA approved a new dosing -- 12 loading dose for Vimpat -- lacosamide. It's not the 13 most dramatic approval ever. But it did use "real- 14 world data," quote/unquote, "real-world evidence" in 15 lieu of a new trial.</p> <p>16 Now, granted, the effectiveness side of 17 the approval was based on extrapolation. But the 18 real-world data were used to be comfortable with a 19 labeling change last year in terms of the age was 20 lowered to 1 month. I think it had been 4 years. I 21 would have to look up the details.</p> <p>22 But just to show that we are committed</p>	<p>1 DR. CONCATO: Yeah. One -- one more 2 repeat. I'll put it in the chat after I'm done 3 speaking. But for those who weren't on the call 4 yesterday, if there's enthusiasm to look at the 5 feasibility of an externally controlled trial, AKA, 6 you know, it doesn't have to be natural history, but a 7 comparator arm from somewhere other -- essentially a 8 single-arm trial and a comparator arm from somewhere 9 else, then our externally controlled trial guidance is 10 the place to look if one is thinking about a 11 regulatory submission.</p> <p>12 And I think we've been pleased by the 13 fact that we're being criticized from both sides. 14 Some saying how could we dare think of doing anything, 15 other than traditional randomized trials, and others 16 saying that we weren't permissive enough and not that 17 everything should fly, but that we -- we basically say 18 the natural history has to be understood.</p> <p>19 I think the problem here is, it's -- 20 it's not a very optimistic starting point. It's no 21 one's fault, but the -- you know, the heterogeneity of 22 the disease, the problem with identifying an outcome,</p>
<p>1 to -- to the appropriate use of real-world data, real- 2 world evidence, but in each context, what RWD/RDE is 3 differs, and at all times, we're not trying to be 4 anything other than protecting the public health by 5 making sure that the evidentiary standard is 6 maintained and as has been mentioned earlier, we 7 clearly are more flexible with rare disease, not by 8 lowering the standard, but by understanding the 9 context that we're in.</p> <p>10 Thank you.</p> <p>11 DR. HODOWANEC: Thank you, John. All 12 very useful comments. I think when we drafted these 13 panel discussion questions, the -- the real-world 14 evidence question, I think we were envisioning more of 15 a discussion about, you know, a historical control, 16 that type of thing, given the -- the issues with 17 having a placebo-controlled trial, given the current 18 landscape.</p> <p>19 But I think as has been raised over the 20 course of today, there are other ways, such as -- as 21 exploring potential safety signals that -- that we 22 could consider leveraging real-world evidence.</p>	<p>1 and also the anticipated effect size, we have more 2 confidence that bias is not going to explain an 3 apparent dissociation.</p> <p>4 If the apparent -- if the expected 5 effect size is large here, I'm not really hearing 6 about, you know, candidate drugs that are -- that are 7 showing promise, but just haven't been vetted through, 8 say, traditional phase 3 trial. Thank you.</p> <p>9 DR. HODOWANEC: Thank you, again, Dr. 10 Concato.</p> <p>11 One sort of related comment that we 12 have in the Q&A is "Have there been efforts in the 13 past, or is there interest moving forward in 14 establishing a registry capable of capturing data from 15 routine clinical practice for infants with congenital 16 CMV?"</p> <p>17 Dr. Bo?</p> <p>18 DR. BO: Yeah. I think along the lines 19 with that question, I'm wondering -- you know, we 20 have -- Dr. Greenberg I recall spoke about -- really 21 greatly -- nicely about the clinical trial network.</p> <p>22 Could that network be leveraged to essentially look</p>

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<p>1 into some of these questions?</p> <p>2 From a public health policy</p> <p>3 perspective, I think what was mentioned was that the</p> <p>4 practice of using drugs for which there isn't an</p> <p>5 official indication for, and could the network</p> <p>6 essentially capture the -- how -- how that -- the</p> <p>7 patterns of practice and outcomes associated with</p> <p>8 those -- with those practices can be qualified.</p> <p>9 DR. GREENBERG: And this is Rachel. So</p> <p>10 we have -- I mean, we definitely explore the use of</p> <p>11 registries and other indications, and so I think that</p> <p>12 is -- is definitely -- definitely possible. I think</p> <p>13 it's in -- where we've explored has been a therapeutic</p> <p>14 area, which was not as much of a rare disease.</p> <p>15 And so, you know, I think to -- to have</p> <p>16 a successful registry here, we'd have to -- we'd have</p> <p>17 to think about the -- the resources.</p> <p>18 I think the PTN specifically has the</p> <p>19 mandate to affect drug labels. And so understanding</p> <p>20 the pathway by which registry data could support a</p> <p>21 change in -- in a drug label is -- would be really</p> <p>22 key.</p>	<p>1 have -- you could capture those and -- and have maybe</p> <p>2 some comparator arm to something captured</p> <p>3 prospectively.</p> <p>4 Dr. Pesch, it looks, like, you'd like</p> <p>5 to weigh in.</p> <p>6 DR. HODOWANEC: Thank you, Dr.</p> <p>7 Greenberg. Yes, thank you, Dr. Greenberg.</p> <p>8 DR. PESCH: Oh, yeah. I just wanted to</p> <p>9 mention that last year, the National CMV Foundation</p> <p>10 was awarded a grant from NORD to create a registry for</p> <p>11 CMV on their IMRARE Platform. And so it's currently</p> <p>12 being designed. I'm on the advisory board. It's not</p> <p>13 launched yet.</p> <p>14 But they -- in terms of the design, I</p> <p>15 think, looking at natural history, as well as family</p> <p>16 impact and some of the psychosocial measures, was the</p> <p>17 initial focus of the registry. But the National CMV</p> <p>18 Foundation was -- is very open to collaborating and</p> <p>19 part of the idea behind this registry is to use it for</p> <p>20 research purposes and have it be flexible.</p> <p>21 So if anyone wants to get in touch with</p> <p>22 me, I can loop you in.</p>
<p>1 But I think such a network that has</p> <p>2 established sites across the country could be an ideal</p> <p>3 setting for the -- building something like this,</p> <p>4 because we have other studies going on that are more</p> <p>5 opportunistic, observational.</p> <p>6 So, you know, if this was realized --</p> <p>7 if it was recognized, could we -- and, you know, have,</p> <p>8 you know, a participant with -- a potential</p> <p>9 participant with congenital CMV, could we capture all</p> <p>10 of those participants at any clinical trials that I</p> <p>11 think -- thinking outside the box, that would be</p> <p>12 really exciting to -- to think about.</p> <p>13 So -- and I think a registry would</p> <p>14 offer the opportunity to capture potentially the</p> <p>15 natural history that is -- we think is really</p> <p>16 difficult to capture.</p> <p>17 So there, you know -- there are</p> <p>18 situations where -- in the current setting, where</p> <p>19 these patients are missed or, you know, they don't --</p> <p>20 especially those with, you know -- it -- it's less</p> <p>21 likely, I think, in moderate to severe congenital CMV.</p> <p>22 But it's possible. And so you could</p>	<p>1 DR. VISWANATHAN: Thank you, to both of</p> <p>2 you, for those comments.</p> <p>3 And I'll just share some of the work</p> <p>4 that we've been doing internally at FDA, just trying</p> <p>5 to understand from our standpoint just doing</p> <p>6 demonstration projects in the space about can you</p> <p>7 really follow patients over time; can you identify</p> <p>8 them in electronic medical records and what not?</p> <p>9 What we have found to really be a</p> <p>10 challenge is because of the multi-disciplinary nature</p> <p>11 of this illness -- of congenital CMV, the medical</p> <p>12 record at one institution tends to be quite</p> <p>13 fragmented, because a child might receive care in --</p> <p>14 primary care in one place, ID care in another place,</p> <p>15 ENT in one place, OT/PT outside of an insurance</p> <p>16 building system, for example, through state or other</p> <p>17 local municipal services.</p> <p>18 And so aggregating the -- the records</p> <p>19 for each individual patient from all those different</p> <p>20 care providers is hard and, therefore, leads to a lot</p> <p>21 of missing data if you go to one -- what we believe</p> <p>22 was one central source.</p>

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<p>1 So it is -- it is a challenge, and --</p> <p>2 and anybody who was trying to undertake building a</p> <p>3 registration, just be aware of that from the outset of</p> <p>4 how many partners you would have to have to get a full</p> <p>5 clinical picture represented.</p> <p>6 DR. HODOWANEC: I'd like to go to</p> <p>7 another question in the Q&A. We talked a little bit</p> <p>8 about PCORI before. But we have a question, "Has</p> <p>9 anyone queried PCORnet?" Does anyone have any</p> <p>10 information on this they'd like to share with the</p> <p>11 group?</p> <p>12 Okay. I'm going to take that silence</p> <p>13 as -- as lack of -- of information on this. And I</p> <p>14 think that's an interesting point for us to consider.</p> <p>15 Any additional comments at this time?</p> <p>16 All right. We're hearing nothing. And I think that</p> <p>17 we can conclude this panel discussion.</p> <p>18 I'd like to give my sincerest thanks to</p> <p>19 all of our panelists for such a wonderful,</p> <p>20 enlightening discussion. And I will now turn it over</p> <p>21 to Dr. Prabha Viswanathan, deputy director in the</p> <p>22 Office of Pediatric Therapeutics, for a few very brief</p>	<p>1 this meeting that we wouldn't end -- we wouldn't</p> <p>2 depart with all the answers -- with having everything</p> <p>3 figured out. But I think we've all learned quite a</p> <p>4 bit, and this will shape our future work.</p> <p>5 One theme that, I think, came through</p> <p>6 both yesterday and today is that collaboration is key.</p> <p>7 And I hope that this -- this conversation and -- and</p> <p>8 this conference has helped bring some people together</p> <p>9 who might be great collaborators in the future. And</p> <p>10 we would like to be part of your ten. So this is our</p> <p>11 declaration that we want to be your partner in</p> <p>12 progress in this field to get drugs for these patients</p> <p>13 who so desperately need them.</p> <p>14 So let me just end by acknowledging a</p> <p>15 few more people. We want to thank our leadership for</p> <p>16 supporting this work in a very challenging area.</p> <p>17 We want to thank our AV team who has</p> <p>18 been outstanding, to -- to Corey and Marcus for making</p> <p>19 this a successful and seamless event, and finally, a</p> <p>20 huge round of applause to Natalie Pica and Aimee</p> <p>21 Hodowanec who have been so generous with their time</p> <p>22 and efforts to make this a successful event.</p>
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<p>1 closing remarks. Thank you, everyone.</p> <p>2 DR. VISWANATHAN: Hello, again. It has</p> <p>3 been a really amazing two days. Obviously, this was</p> <p>4 difficult work. We knew that going into this. And we</p> <p>5 appreciate the attention, the time that you've all</p> <p>6 taken to participate in this conversation yesterday</p> <p>7 and today.</p> <p>8 So first, let me thank all the speakers</p> <p>9 for providing very enlightening talks, setting the</p> <p>10 stage for great discussions. And thank you to our</p> <p>11 panelists who were -- have been generous with your</p> <p>12 thoughts, your opinions and ideas, which is exactly</p> <p>13 what we were looking for in this forum.</p> <p>14 I always want to thank all of our</p> <p>15 attendees. Some of you are thought leaders in this</p> <p>16 field as well. We hope that you gain some -- some</p> <p>17 insight to take forward in your future endeavors in</p> <p>18 this space.</p> <p>19 And to those who are new to the space,</p> <p>20 welcome to our -- to our -- our camp here. We are</p> <p>21 happy to -- to collaborate with you in the future.</p> <p>22 I think we all knew when we convened</p>	<p>1 So with that, we will adjourn. We wish</p> <p>2 you well in all your great work and hope to see you</p> <p>3 all soon in forums such as this.</p> <p>4 Please, don't hesitate to reach out</p> <p>5 with questions or comments. We will be updating the</p> <p>6 meeting website with materials, including slides and a</p> <p>7 transcript, hopefully in the -- in the near future.</p> <p>8 So please, be on the lookout with that -- for that.</p> <p>9 With that, we'll say our goodbyes.</p> <p>10 Thank you, so much, everyone.</p> <p>11 UNIDENTIFIED SPEAKER: Thank you.</p> <p>12 Thank you, so much.</p> <p>13 DR. BO: Thank you. Thank you, very</p> <p>14 much.</p> <p>15 DR. VISWANATHAN: Everyone. Thank you.</p> <p>16 Bye.</p> <p>17 (Whereupon, the meeting concluded at</p> <p>18 3:23 p.m.)</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>

1 CERTIFICATE 2 I, ALEXANDRA HOBRECHT, the officer before 3 whom the foregoing proceedings were taken, do hereby 4 certify that any witness(es) in the foregoing 5 proceedings, prior to testifying, were duly sworn; 6 that the proceedings were recorded by me and 7 thereafter reduced to typewriting by a qualified 8 transcriptionist; that said digital audio recording of 9 said proceedings are a true and accurate record to the 10 best of my knowledge, skills, and ability; that I am 11 neither counsel for, related to, nor employed by any 12 of the parties to the action in which this was taken; 13 and, further, that I am not a relative or employee of 14 any counsel or attorney employed by the parties 15 hereto, nor financially or otherwise interested in the 16 outcome of this action.  17 ALEXANDRA HOBRECHT 18 Notary Public in and for the 19 State of Michigan 20 21 22	Page 586
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