Controversies in the Diagnosis and Treatment of Cytomegalovirus Induced Hearing Loss

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HEALTH

UNIVERSITY OF UTAH

Nondisclosure:

- NIH U01 PI CMV multi-institutional study
- NIDCD R01 co-I Cochlear Implantation
- Valganciclovir – not FDA approved for congenital CMV

Objectives:

- Convince you that CMV is an important topic yet awareness low
- Story of DD
- Epidemiology of cCMV induced hearing loss
- Rationale for diagnosis
- Treatment
- Changing landscape of screening
- What steps you can do
- One interesting research path

Acknowledge:

- ValEAR Team (UCSD)
- Daniela Carvalho (site PI)
- Julie Stickland (audio)
- Alice Dong (site co-PI)
- Jane Duong (Pharmacy)
- Hena Din (Research Coordinator)

Knowledge Amongst Hearing Specialists:

- Expect those who treat pediatric hearing loss should have high fund of knowledge
- Email list serve ASPO and AOS
- 70 respondents
- 100% familiar with CMV
- 83% evaluate and treat pediatric SNHL

Nagy C, Park A,Tomlinson J, Dedhia K. Awareness of Congenital Cytomegalovirus and its Effects on Hearing Loss among Pediatric Otolaryngologists and Neurootologists. ASPO 2018

Which of the following are routes of transmission for CMV? (Pick all that apply)	Number	%
Kissing	42	61%
Changing diapers	32	46%
Breast milk	37	53%
Blood transfusion	43	61%
Sexual Intercourse	36	51%
Sharing food with children	33	47%
I do not know	20	29%

- **41% more than 80% correct**
- **56% more than 50% correct**
- **20% with 0 correct**

Which of the following statement(s) regarding cCMV is/are true? (pick all that apply)	Number	%
True		
Up to 15% of children with asymptomatic cCMV can develop hearing loss	27	39%
Up to 75% children with symptomatic cCMV will develop hearing loss	21	30%
cCMV is the most common environmental cause of hearing loss	33	47%
False		
Up to 30 % of children with asymptomatic cCMV can develop hearing loss	24	34%
Up to 95% of children with symptomatic cCMV will develop hearing loss	5	7%
I do not know	14	20%

- 23% had at least 75% correct answers
- 54% at least 50% correct

What test(s) can be performed to diagnose cCMV status? (Pick all that apply)	Number	%
True		
Dried blood spot CMV PCR at any age	23	33%
Dried blood spot (DBS) prior to 3 weeks of age	28	41%
Urine PCR/culture prior to 3 weeks of age	44	63%
Saliva CMV Culture with confirmation with Urine PCR/Culture prior to 3 weeks of age	44	63%
False		
Serologic CMV IgG testing at any age	11	16%
Urine PCR/culture at any age	10	14%
Saliva CMV Culture at any age	6	9%
Serologic IgM testing at any age	7	10%
I do not know	**14**	**20%**

Which test(s) can definitively establish a diagnosis for cCMV in children >3 weeks of age?	Number	%
True		
Dried blood spot testing	25	36%
False		
Serology for IgM and IgG for CMV	27	39%
Imaging studies including CT and MRI	9	13%
Urine PCR/culture for CMV	16	23%
Saliva culture for CMV	8	11%
I do not know	20	29%

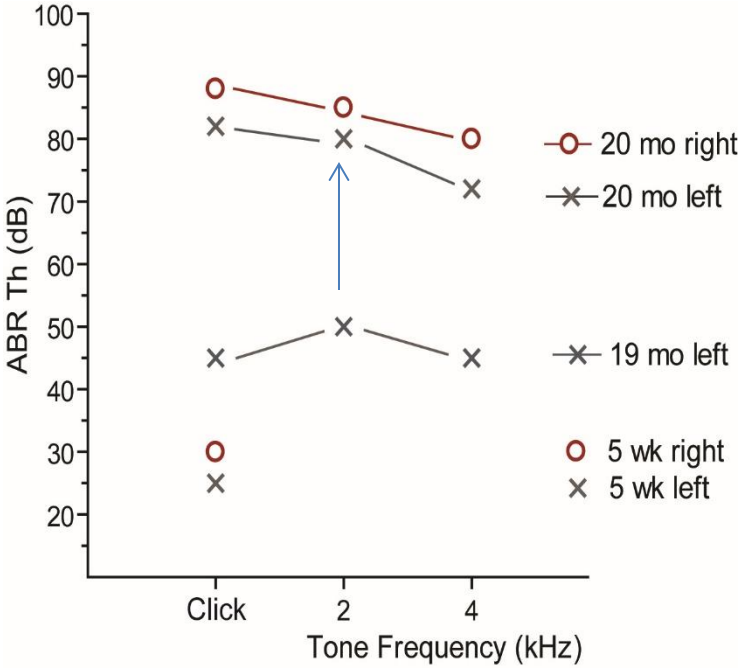
Practice Patterns	Number	%
Do you incorporate any type of cCMV testing for children with SNHL?		
Always	8	11%
Sometimes	22	31%
Rarely	20	29%
Never	20	29%
Do you offer DBS CMV PCR testing for your patients?		
Yes	16	23%
No	52	76%
Do you offer antiviral therapy or refer to infectious disease specialist for antiviral therapy for cCMV infected children?		
Yes, only if they are symptomatic	15	21%
Yes, for symptomatic children and asymptomatic children that fail the hearing screen	28	40%
No	12	17%
I don't know	15	21%

The Story of DD and Hearing Targeted CMV Screening in Utah:

- 19 mo child progressively worsening hearing
- Failed newborn hearing screen and automated ABR
- Click ABR at 3 weeks: 30 dB nHL right and 25 dB nHL left
- Audiology recommended FU 9 mo.
- Enlarged ventricles 34 wks gestation in utero U/S
- U/S at birth- “germinolytic” cystic changes- in utero insult

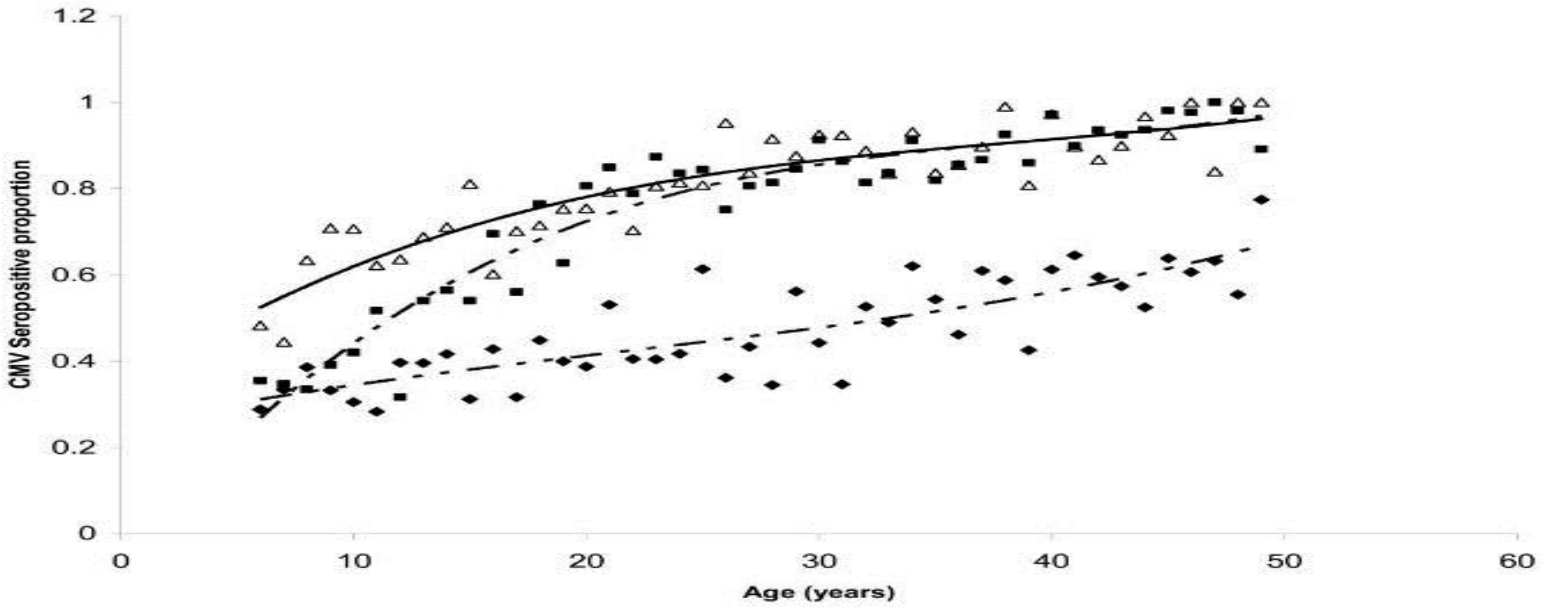
Case History DD and Utah CMV Screening:

- Normal Otologic examination
- Repeat ABR right profound and left moderate SNHL
- Saliva Cytomegalovirus (CMV) PCR- positive
- Neonatal Dry Blood Spot CMV PCR- positive
- 6 week course of valganciclovir
- Left ear worsened to profound
- Bilateral Cochlear Implantation
- Explanted and reimplanted 2 years later



Public Health Impact of CMV

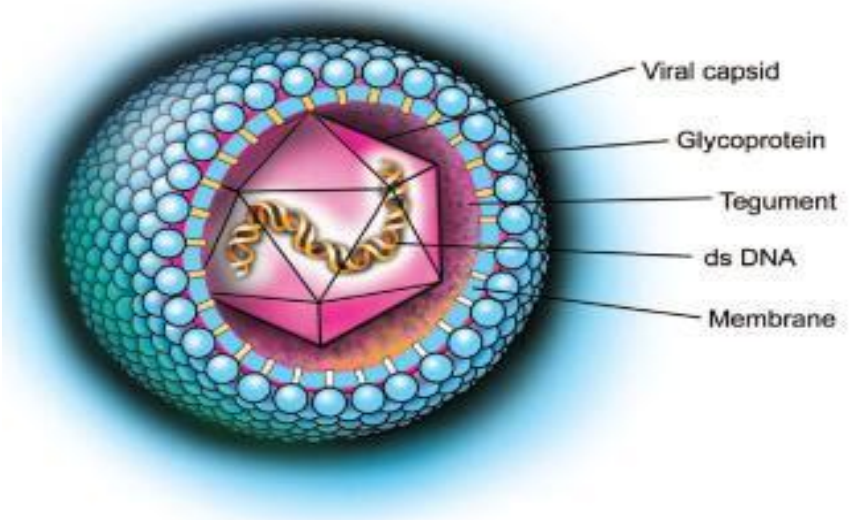
- Herpes virus
- Seroprevalence 50 – 90% of adults
- Increases with age
- Varies btw and within populations



Colugnati et al. BMC Infectious Diseases 2007 **7**:71

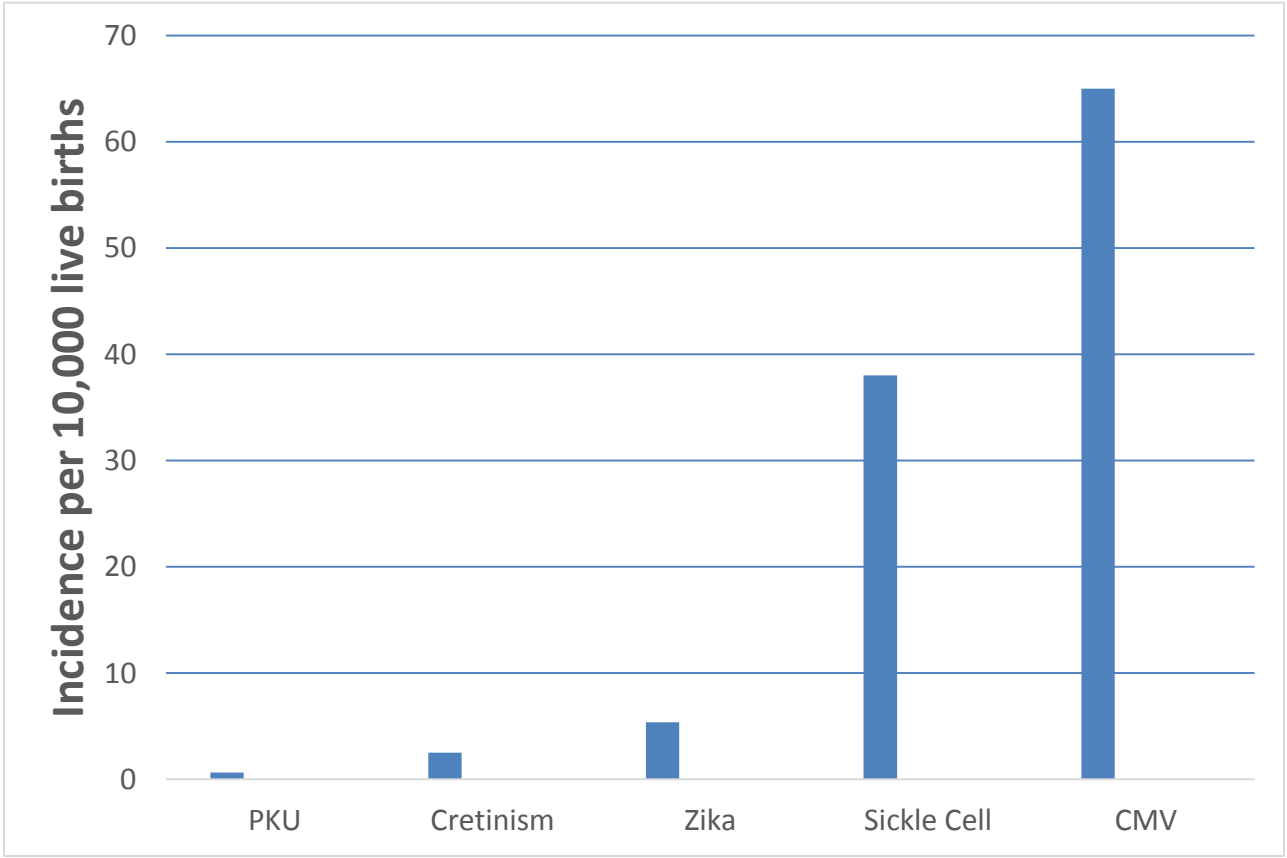
Public Health Impact of CMV

- Species specific (only infects humans)
- Most common congenital infection worldwide- 0.7% ALL live births
- Most common cause of nonhereditary SNHL
- May account up to **20%** pediatric SNHL
- Cost C-CMV greater than $ 4 billion/year in US



HCMV Human Cytomegalovirus

Incidence of Congenital Conditions



"Higher risk of Congenital CMV infection that all 29 screened neonatal diseases combined"

Overall risk of CNS complications related to congenital infections

Congenital CMV

- LOW prevalence population - 1 / 1,000 live births
- HIGH prevalence population - 1 / 270 live births

Zika virus

- Brazil - 1 / 800 live births
- US - 1 / 71,684 live births

(102 reported Zika cases to CDC out of 7.9 million live births 2016-2017)

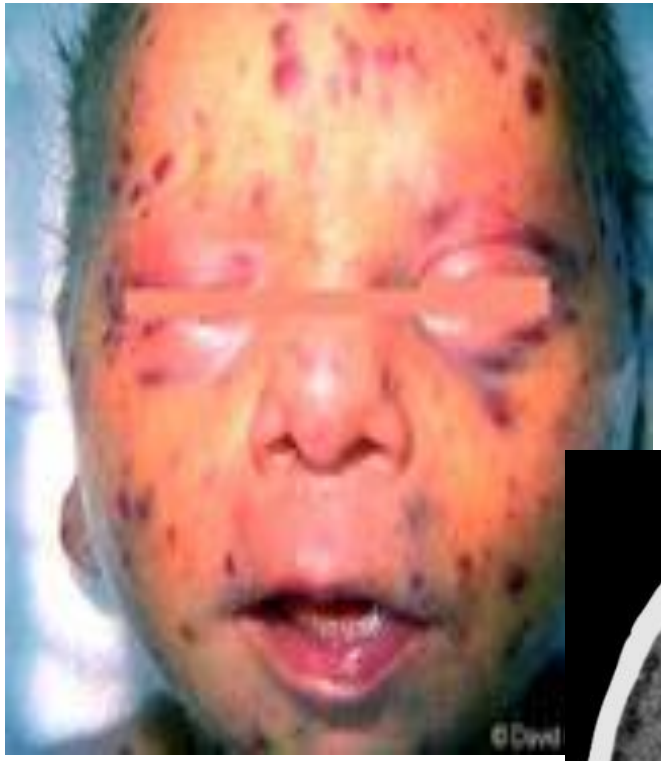
US Congress funded $1.1 Billion for Zika Research and Prevention Sept 2016

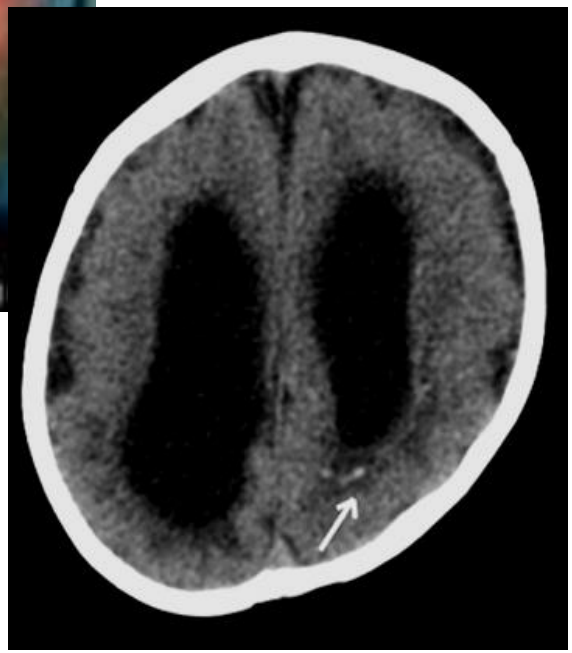
Transmission Mother to Fetus:

- Seronegative moms (Primary infection)
- Seropositive moms (Secondary infection)
- Infant presentation
  - Symptomatic (evident at birth)
  - Asymptomatic (silent at birth)
  - CHIP (CMV infected Hearing Impaired Person)

CMV: Symptomatic Congenital Infection

- Approximately 10%
- Fetal demise
- Prematurity
- Common features:
  - Hepatomegaly
  - Splenomegaly
  - Petechiae
  - IUGR
  - Jaundice
  - Microcephaly
  - Chorioretinitis
  - Sensorineural hearing loss (50%)





CMV: Asymptomatic Congenital Infection

- Approximately 70%
- No signs or symptoms

CHIP: CMV Hearing Impaired Only Person

- **CHIP**: 5- 15% have sensorineural hearing loss that can be evident at birth or appear **later** in childhood

Transmission:

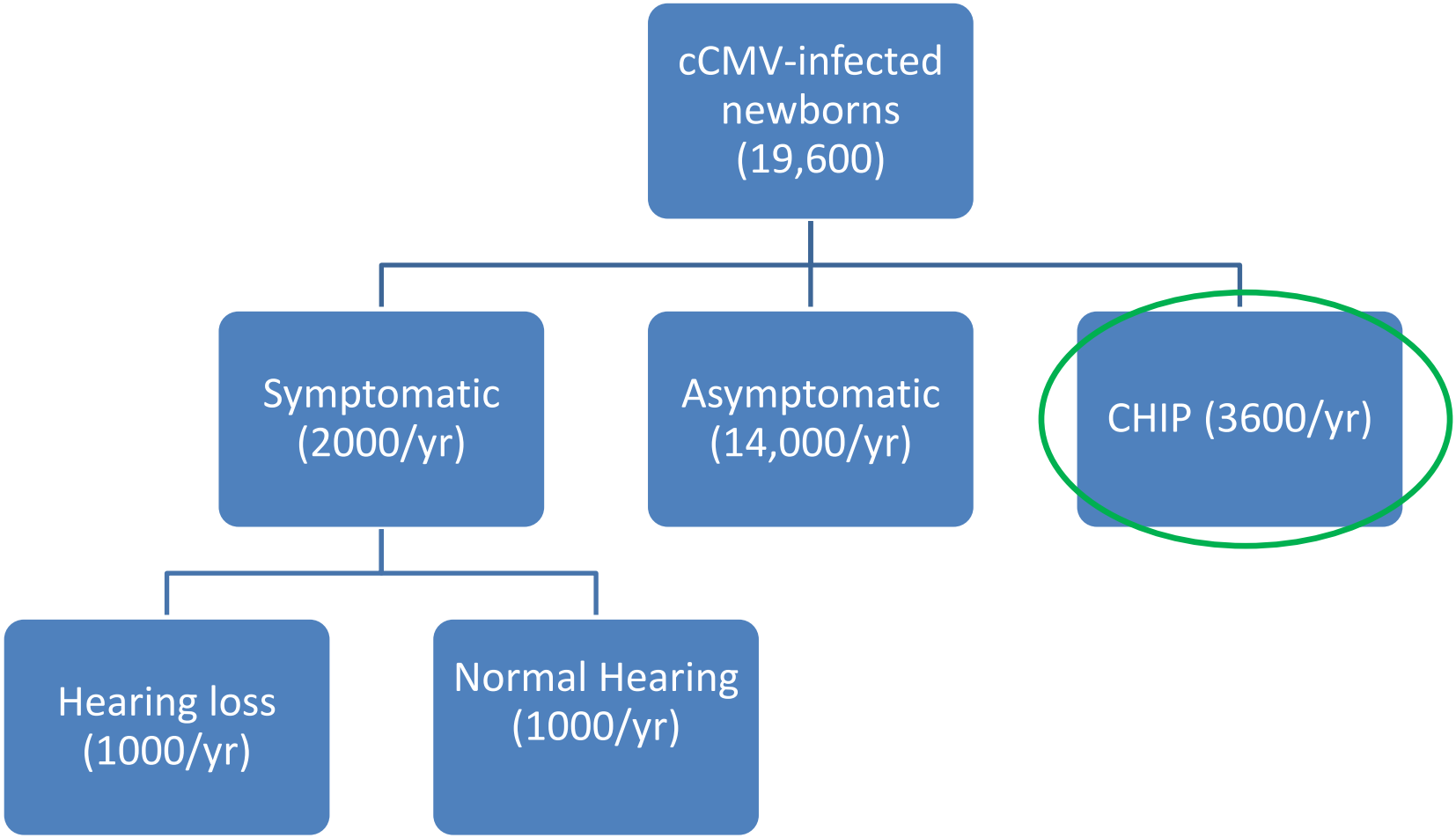
- Child with congenital CMV will shred virus for months or years- “contagious”
- Transmission body fluids
- Pregnant moms or immunocompromised patient at risk for cCMV
- Classic- toddler gets infection daycare then shares it with pregnant mom
- Hand washing, avoid kissing on lips, no sharing utensils
- 5000 seronegative pregnant women – behavioral intervention > 50% drop expected rate seroconversion

Vauloup-Fellous et al, 2009

Hysteria of CMV:

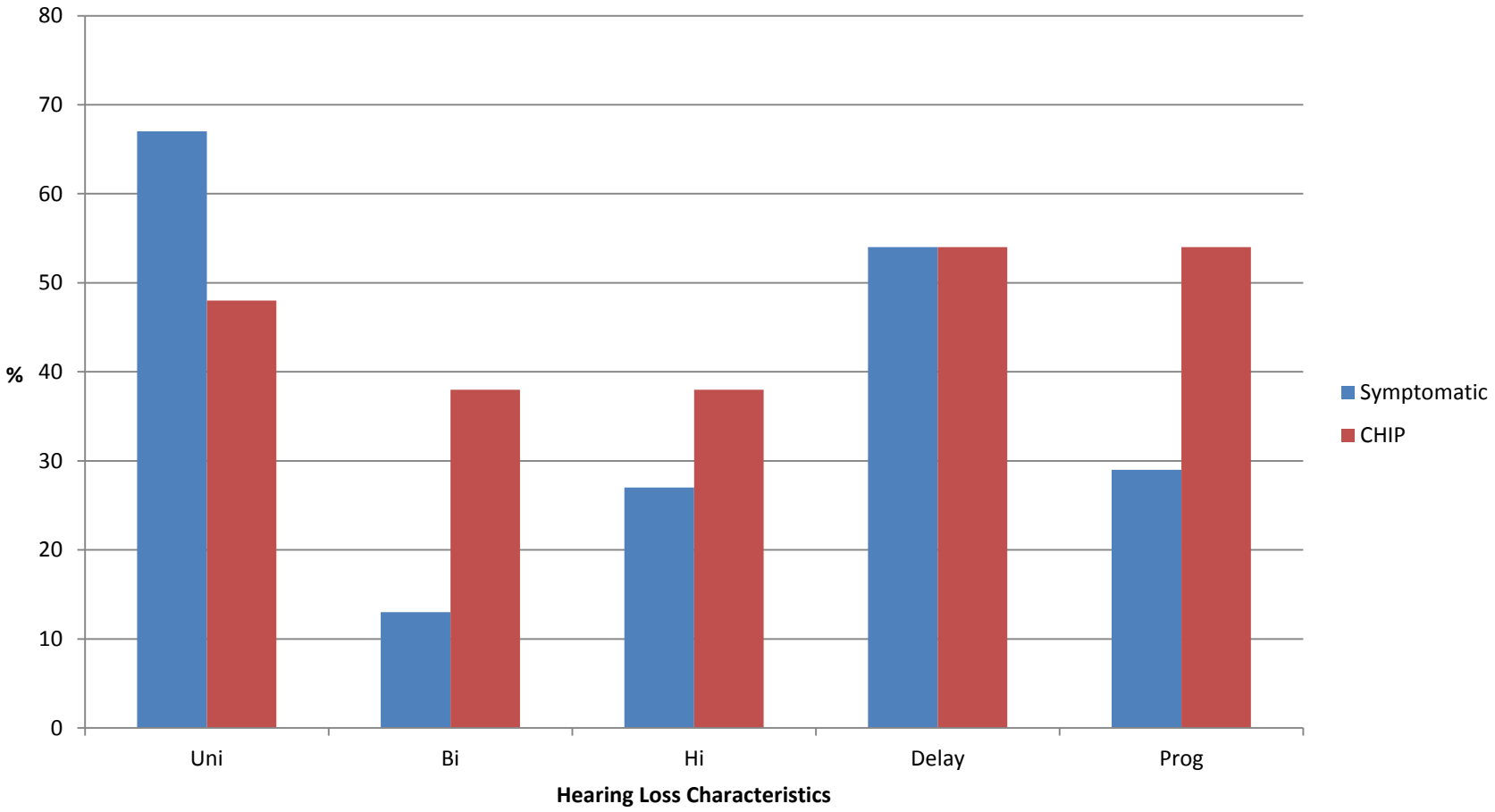
- Audiologists not want to test cCMV infected kids
- Daycare and Schools not wanting to allow cCMV infected kids to attend
- Not the recommendation National CMV Foundation!
- Any child or adult may be seropositive
- Academy position statement

Hearing Loss Disease Burden Symptomatic Asymptomatic CMV and CHIP in the US (annual):



Modified from Cannon MJ et al. Universal newborn screening for congenital CMV Infection: what is the evidence of potential benefit? Rev Med Virol 2014.

Characteristics of CMV Induced Hearing Loss:



Modified from Dahle AJ et al. Longitudinal Investigation of Hearing Disorders in Children with Congenital Cytomegalovirus. J Am. Acadm Audiol 2000; (11) 283-290.

CMV Diagnosis:

- Best if testing when child less than 2-3 weeks of age
- Postnatal infection not associated with hearing loss
- Serology – confounding from maternal IgG and IgM- poor sensitivity
- Urine culture or PCR. Saliva- breastmilk contamination
- Positive DBS definite for CMV but poor sensitivity

Saliva vs Urine for CMV Screening:

- Two large studies indicate high false positive rate with saliva PCR testing
- Saliva obtained immediately after birth
- 26-41% false positive
- Associated with lower viral load BUT low viral load seen in both true positive and false positive samples
- **If you obtain a positive saliva PCR result, you should obtain a confirmatory urine PCR before the child is 3 weeks of age**
- **Consider just ordering a urine CMV PCR**

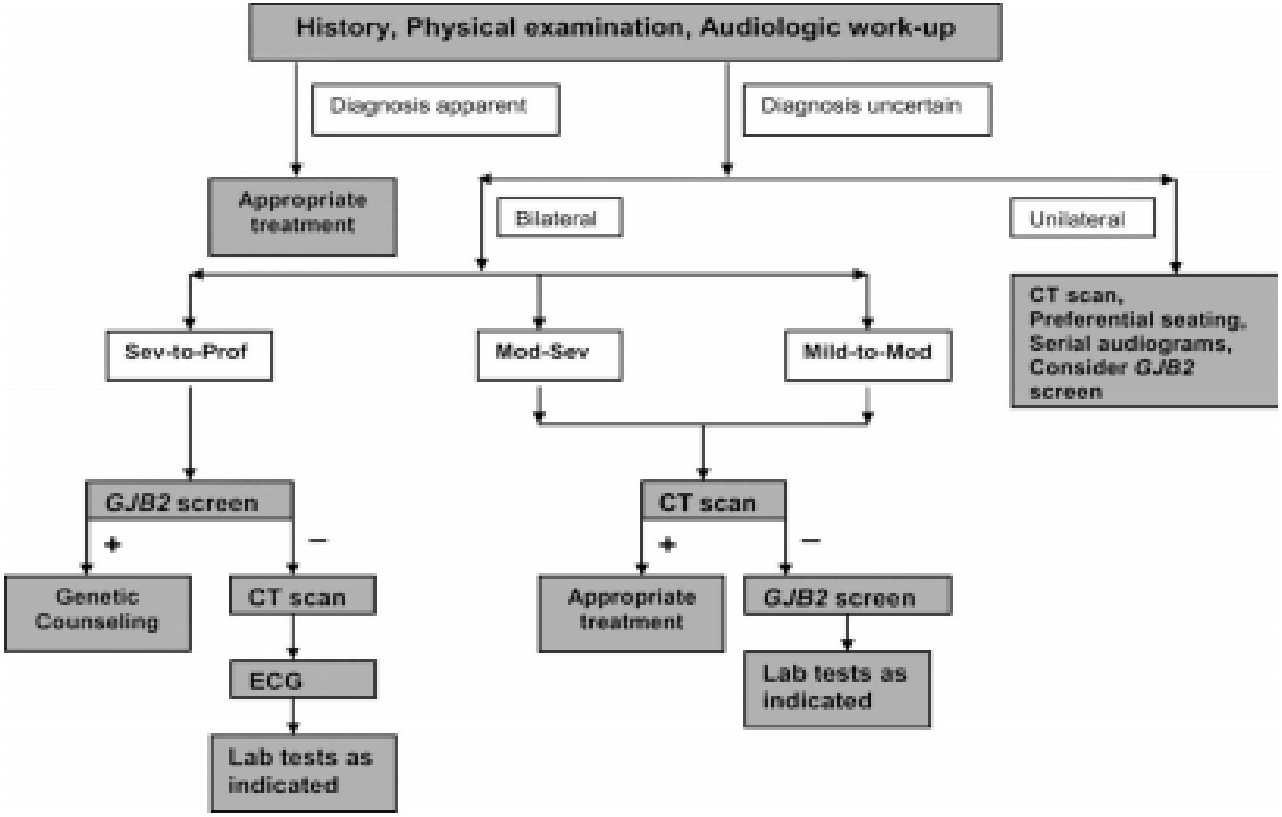
Puhakka et al. JPIDS 2018; Leruez-Ville et al. Clin Infect Dis 2017

What is the Sensitivity of DBS Testing?

- CHIMES March 2007-2008
- 7 US Medical Centers
- Compared saliva rapid culture to DBS CMV PCR (single and double primer)
- 92/20,448 infants CMV based on saliva cx
- Sensitivity DBS:
- Single primer- 28.3%
- Double primer- 34.4%
- **Should have compared to urine culture or PCR testing?**
- **Schleiss and Dollard CDC study on DBS**

Boppana S et al. JAMA 2010; 303(14): 1375-1382.

Role of CMV Testing in Pediatric Hearing Loss:



Preciado DA et al. Improved Diagnostic Effectiveness with a Sequential Diagnostic Paradigm in Idiopathic Pediatric Sensorineural Hearing Loss. Otol and Neurotology 2005

Role of CMV Testing in Pediatric Hearing Loss:

THE Laryngoscope
FOUNDED IN 1896
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Triological Society Best Practice

What is the optimal workup for a child with bilateral sensorineural hearing loss?†

Catherine K. Hart MD ✉, Daniel I. Choo MD

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BACKGROUND

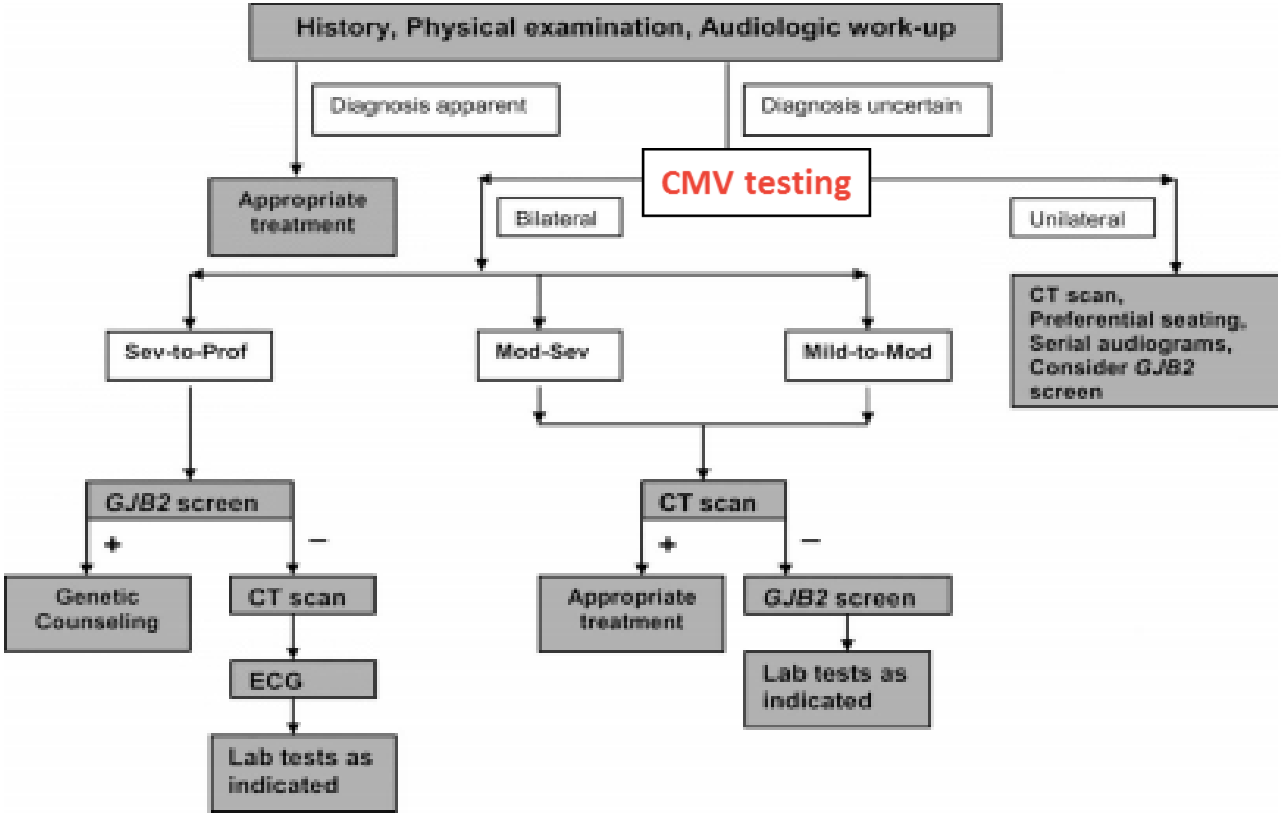
In the United States and other developed countries, approximately one to two children per 1,000 have moderate to profound bilateral sensorineural hearing loss (SNHL).1 SNHL can be broadly classified as hereditary, acquired, or idiopathic. Up to 35% of children with SNHL have a history suggestive of acquired environmental etiology.1 Physical examination can reveal dysmorphic features suggestive of syndromes that are associated with SNHL. However, in the majority of children, history and physical examination alone will not reveal the cause of SNHL. The practitioner is then faced with a plethora of diagnostic options to determine the etiology of the SNHL.

In addition to a complete history, physical examination, and audiometric testing, the evaluation of bilateral pediatric SNHL has typically included a comprehensive battery of laboratory tests, radiologic studies, electrocardiogram (ECG), and more recently, genetic testing, as well as ophthalmology evaluation and referral to a clinical geneticist. The necessity of exhaustive testing remains controversial, and recent studies have demonstrated that a sequential diagnostic algorithm is sensitive and clearly more cost-effective than a comprehensive testing approach.

LITERATURE REVIEW

Hart C and Choo D. Laryngoscope. 2013

Role of CMV Testing in Pediatric Hearing Loss:



Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Chart and database review
- Children 3 yrs or younger
- May 2008-September 2013
- Sequential diagnostic paradigm

Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Those with negative CMV testing underwent imaging, genetics evaluation +/- EKG
- Cost analysis of the diagnostic testing (Multihospital Standardized Cost Accounting System):

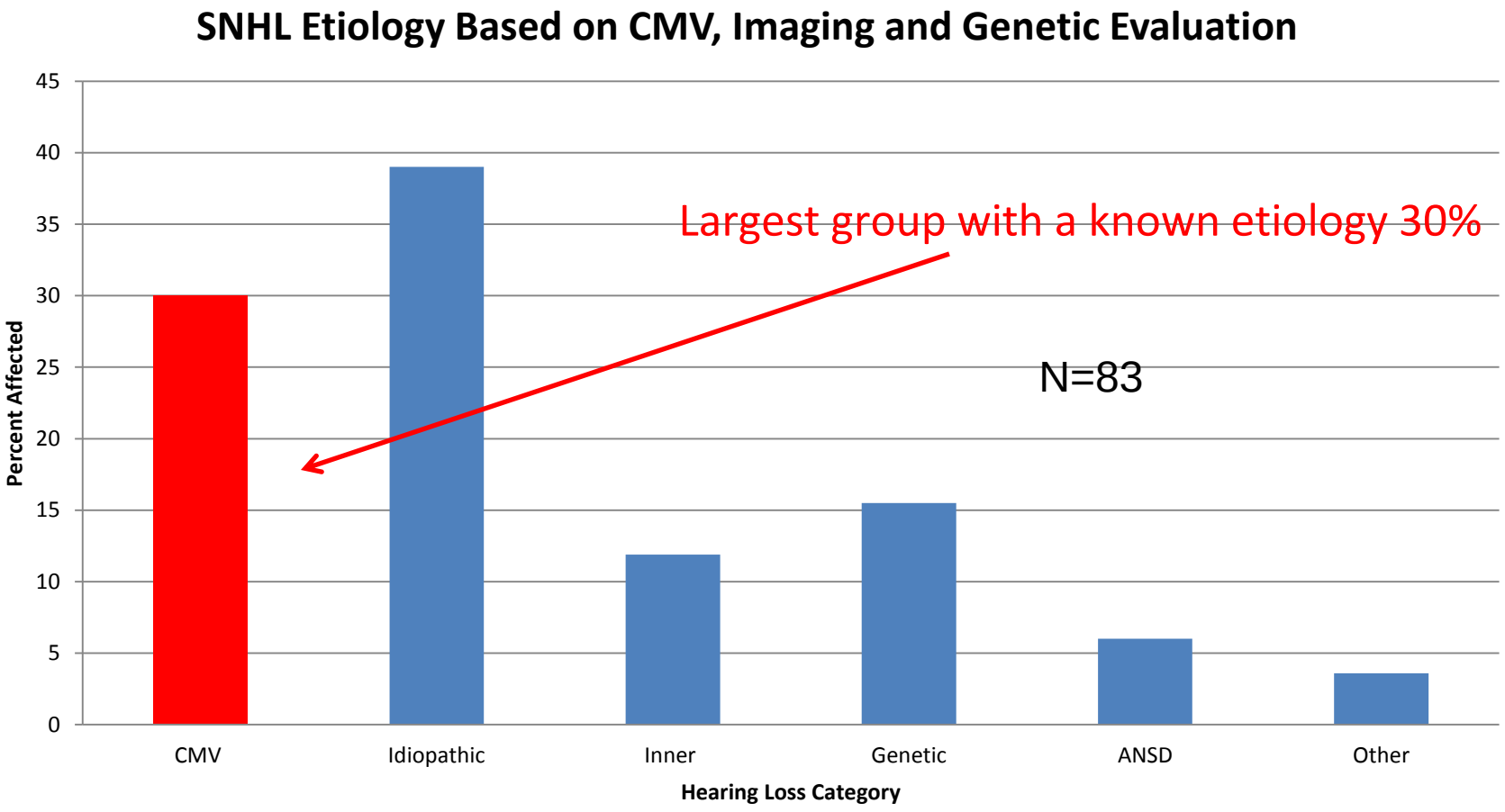
  MRI t-bone $1591

  GJB2 testing $611

  CMV PCR saliva or urine $66

Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss



Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Breakdown of CMV Patients (n=25)
- Sixteen – confirmed CMV diagnosis
- Six of sixteen diagnosed via DBS testing
- Nine- probable CMV diagnosis

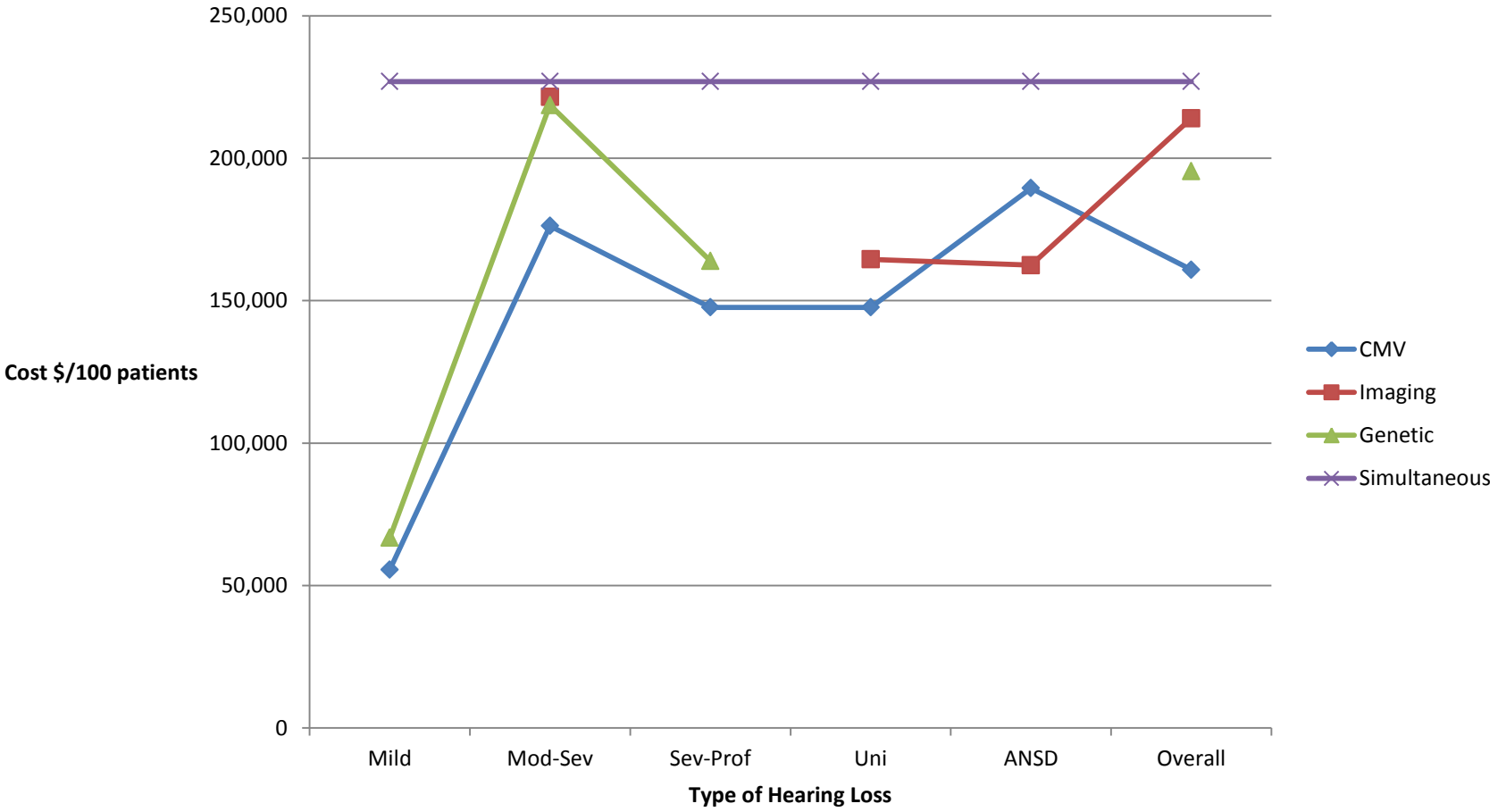
Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- <u>Characteristics of CMV Induced SNHL Patients:</u>
- Average age initial evaluation 352 days (range 24-1387 days)!
- Only 5 infants evaluated at one month of age or younger

Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

Cost Estimates Using Different Approaches for SNHL Evaluation:



Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Conclusion:
- Diagnostic Paradigm incorporating early CMV testing has high yield (30%)
- DBS testing can diagnose infants > 3 weeks of age
- Average age of initial evaluation significant challenge for diagnosis
- Early CMV testing – lower cost than imaging or genetic testing

Role of CMV Testing in Pediatric Hearing Loss:

< Previous Article | November 2016 Volume 90, Pages 251–258 | Next Article >

International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient

Bryan J. Liming, John Carter, Alan Cheng, Daniel Choo, John Curotta, Daniela Carvalho, John A. Germiller, Stephen Hone, Margaret A. Kenna, Natalie Loundon, Diego Preciado, Anne Schilder, Brian K. Reilly, Stephane Roman, Julie Strychowsky, Jean-Michel Triglia, Nancy Young, Richard J.H. Smith

PlumX Metrics

DOI: http://dx.doi.org/10.1016/j.ijporl.2016.09.016 | CrossMark

Article Info

Abstract | Full Text | Images | References

Abstract

Objective

To provide recommendations for the workup of hearing loss in the pediatric patient.

Methods

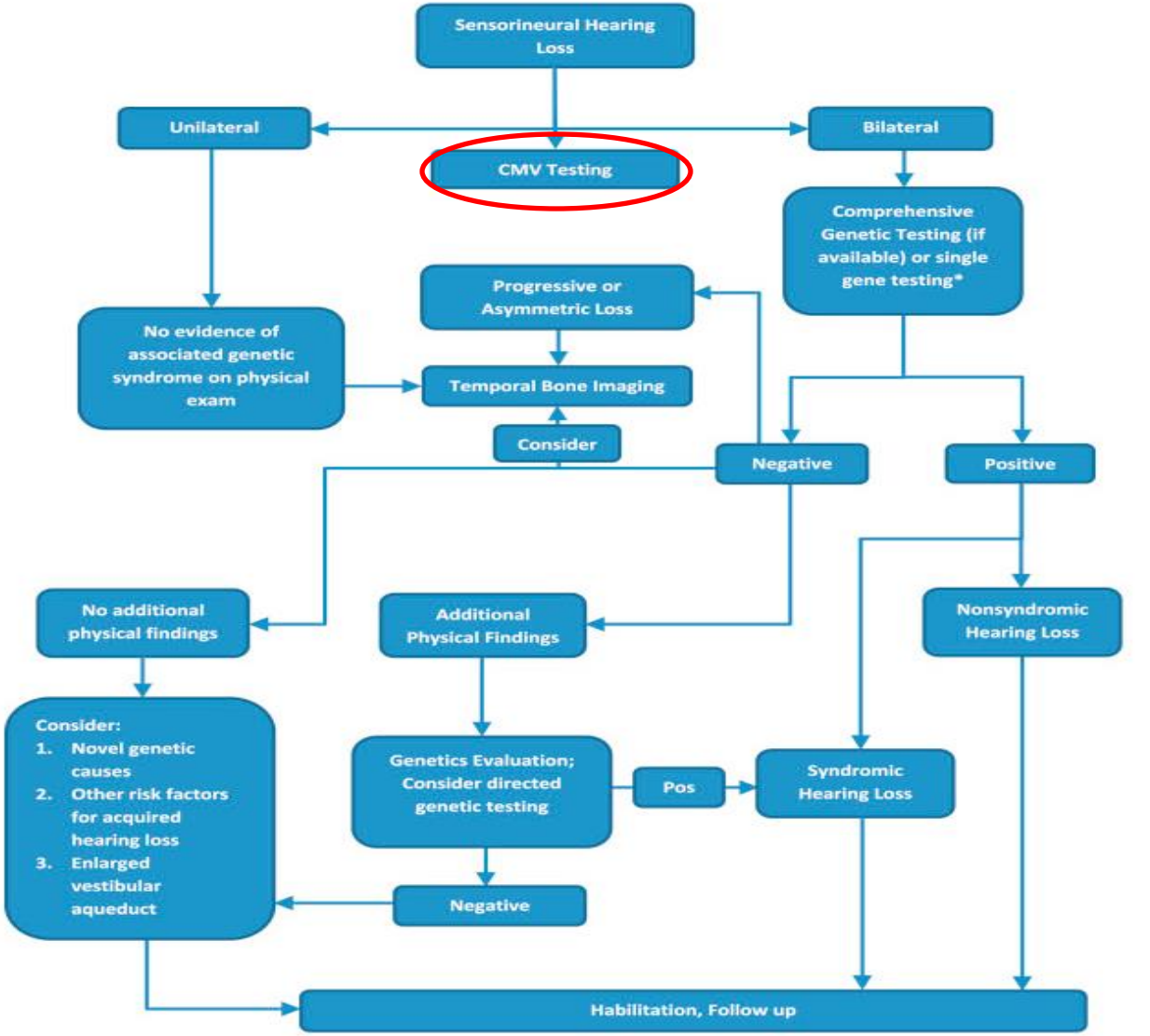
Expert opinion by the members of the International Pediatric Otolaryngology Group.

Results

Consensus recommendations include initial screening and diagnosis as well as the workup of sensorineural, conductive and mixed hearing loss in children. The consensus statement discusses the role of genetic testing and imaging and provides algorithms to guide the workup of children with hearing loss.

Conclusion

The workup of children with hearing loss can be guided by the recommendations provided herein.



Liming BJ et al. Int. Ped. Otolaryngology Group. Int J Peds Oto 2016

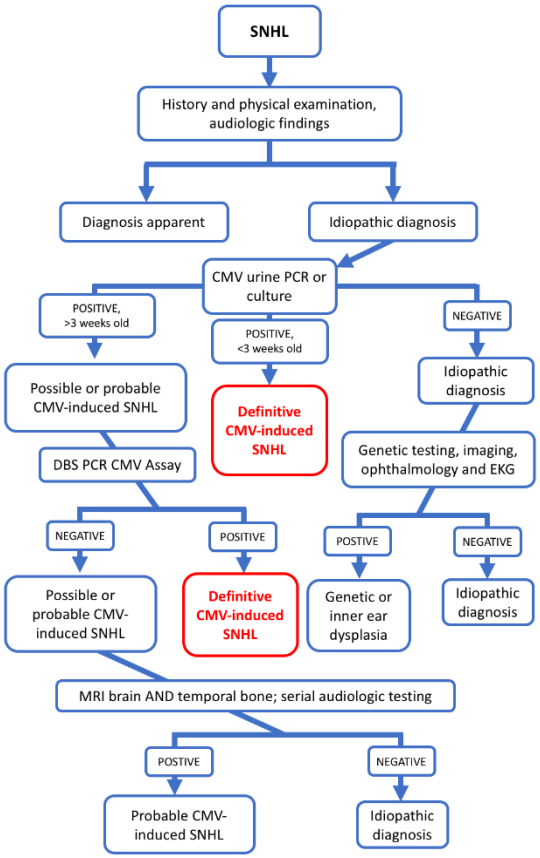
DD=Daisy Doutre

Sara Doutre
Board National
CMV Foundation

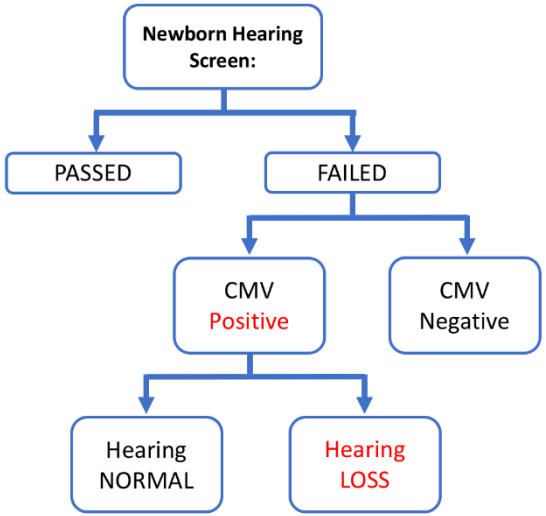
Former Representative
Ronda Menlove

Challenge of CMV testing in the "Older" (> 3 weeks) Hearing Impaired Child:

Without HT-CMV



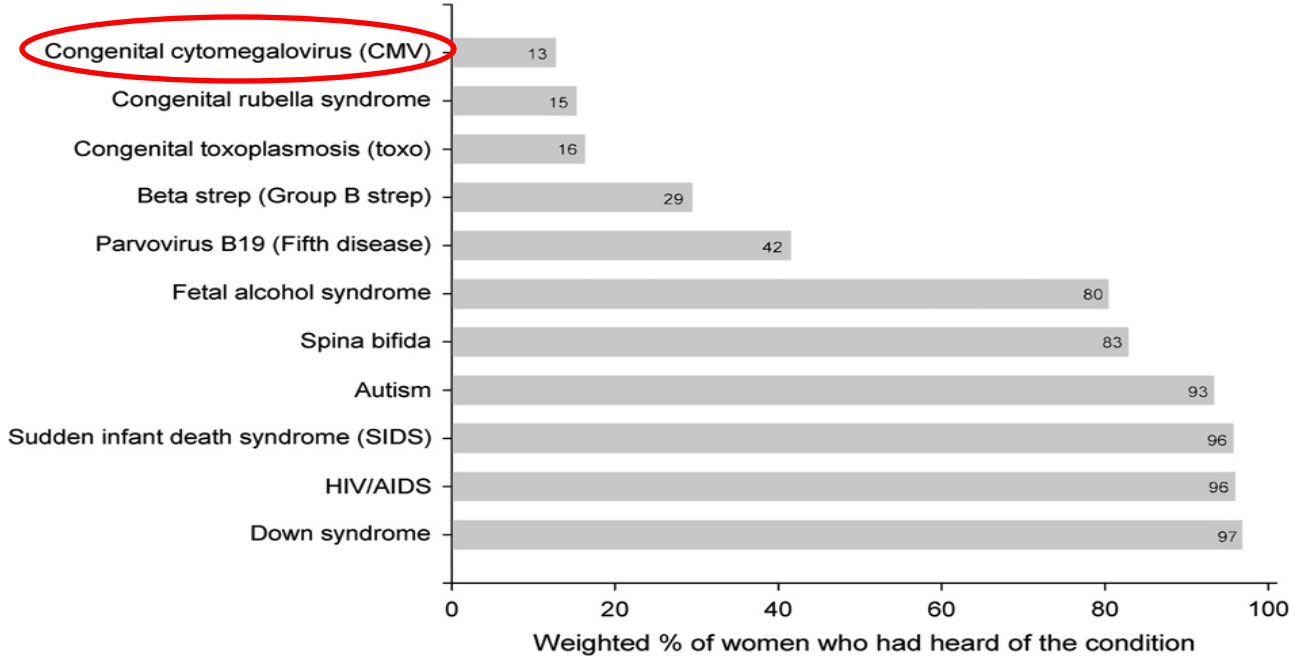
With HT-CMV



Park et al. A Diagnostic Paradigm Including Cytomegalovirus Testing for Idiopathic Pediatric Sensorineural Hearing Loss. Laryngoscope. 2014

Awareness of CMV:

- National survey 4184 participants (HealthStyles survey)
- 7% men and 13% women had heard of CMV



Cannon MJ, et al. Awareness and behaviors related to child-to-mother transmission of cytomegalovirus. Preventive Medicine 2012.

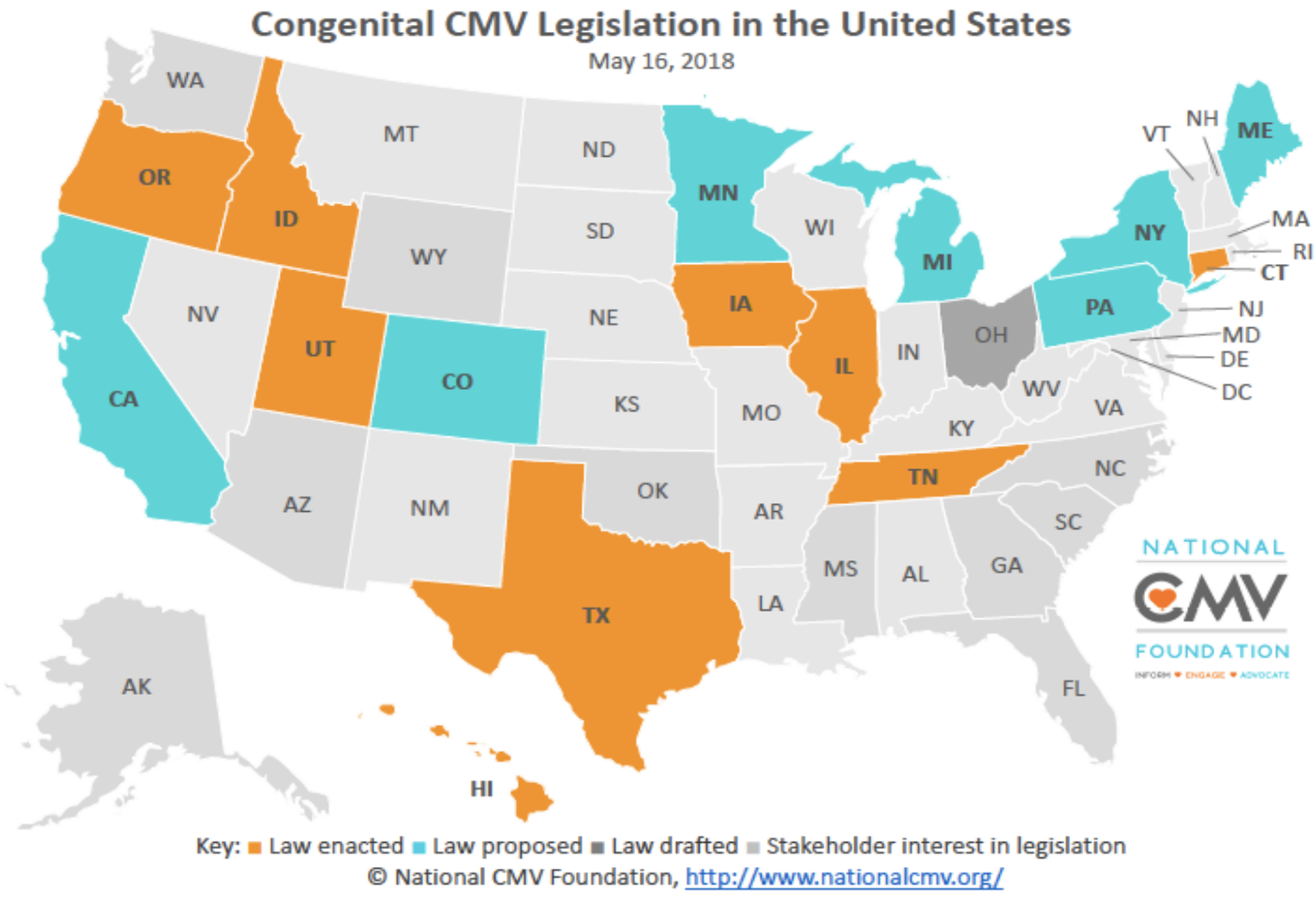
Utah Legislative Efforts:

Utah House Bill 81 (July 2013):

- DOH public education program to inform caregivers about CMV
- DOH education for providers and other organizations offering children's programs
- Medical practitioners to test infants < 3 wks of age who fail two newborn screening tests for CMV and inform the parents cx and rx

National Map for Hearing Targeted Early CMV Screening (HT-CMV) 2013:

National Map for Hearing Targeted Early CMV Testing (HT-CMV)2018:



AAP Newsletter:

- December 2015
- Department Practice and Division of Quality
- Response to legislative efforts on CMV Testing for newborns who fail an infant hearing test

AAP Newsletter:

- “No evidence … supports treatment of newborns who test positive for CMV but are otherwise asymptomatic…”

AAP Newsletter:

- “Treatment currently is limited to off-label use of the antiviral drug valganciclovir which carries potential risks”

AAP Newsletter:

- “Clinicians practicing in the best, most up-to-date fashion … face increased medical practice liability risk. If states continue down this path, it may threaten our ability to practice medicine in a manner consistent with the best available science…”

AAP Views:

- “These kinds of laws… may drive such treatment …parents and providers often will feel that they must do something…In so doing, we may harm the children we are trying to help…”

What is Treatment?

- **treatment** [trēt´ment]
- **1.** the management and care of a patient; see also CARE.
- **2.** the combating of a disease or disorder; called also therapy.

Treatment Does Not Need to Mean Just Antiviral Therapy!

The Evidence for HT-CMV Screening is…

- Helps the family of hearing impaired child
- Increases Detection rate of **Symptomatic** CMV infected children
- Focuses attention on CMV infected infants for progressive hearing loss
- Improves time to diagnose hearing loss for all newborns who fail their hearing screen
- May improve hearing outcomes of CMV hearing impaired infants

Helping the Family:

“Blindness separates people from things; deafness separates people from people.”

Helen Keller

Helping the Family:

- Parental response – surprise, sadness and concern

- Questions- cause of the hearing loss, likely impact on new family member, options for treatment

Kurtzer-White & Luterman, 2003; Yoshinaga-Itano & DeUzcategui, 2001; Young & Tattersall, 2007

Helping the Family even if the child doesn't present with hearing loss:

- " I would want to have my baby tested for CMV even if my doctor or hospital didn't do it routinely." (84%)
- "I would want to know if my child has CMV even if he or she never develops problems." (84%)
- "I would be willing to pay $20 to have my baby tested for CMV." (87%)

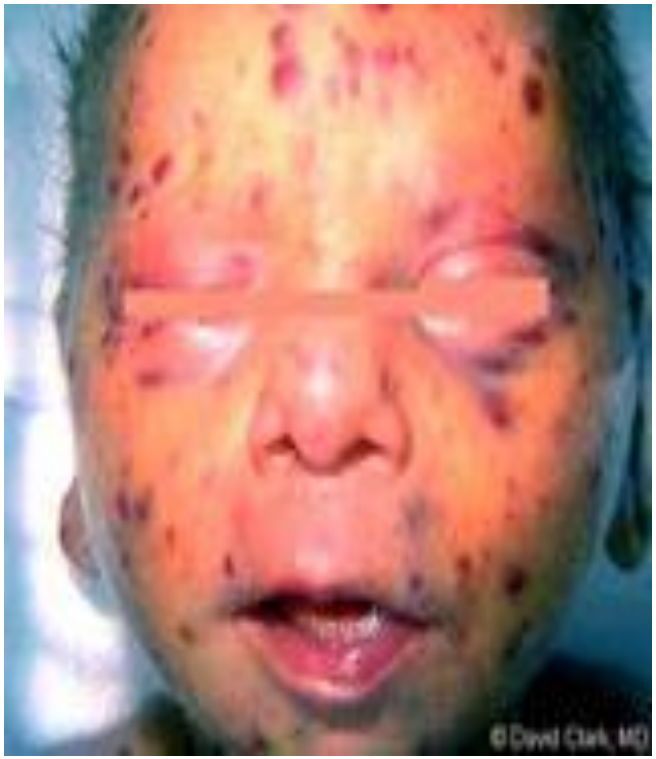
Din E, et al. Attitudes Toward Newborn Screening for Cytomegalovirus Infection. Pediatrics. 2011

Helping the Family:

- CMV testing requires child must be less than **3 weeks** of life!
- Unlike Genetic testing, you cannot decide to wait until the child is older to make the diagnosis
- Families want testing and are willing to pay for it.

Increasing the Detection Rate of the Symptomatic CMV Infected Infant:

- 10% fetal demise
- Prematurity
- Common features:
  - Hepatomegaly
  - Splenomegaly
  - Petechiae
  - Jaundice
  - Microcephaly
  - Chorioretinitis
  - Sensorineural hearing loss (50%)



Increasing the Detection Rate of the Symptomatic CMV Infected Infant:

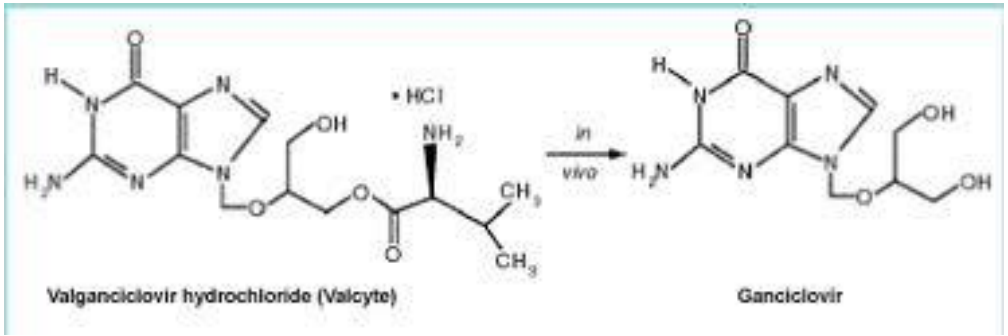
- Minority symptomatic CMV cases diagnosed clinically!
- Vaudry et al., 2014; Townsend et al., 2011; McMullan et al. 2011
- <10% (Sorichetti et al. 2015)

Treating the Symptomatic cCMV Infected Infant:

- Symptomatic CMV is treatable!
- General consensus that this group would benefit from antiviral therapy (valganciclovir or VGCV)

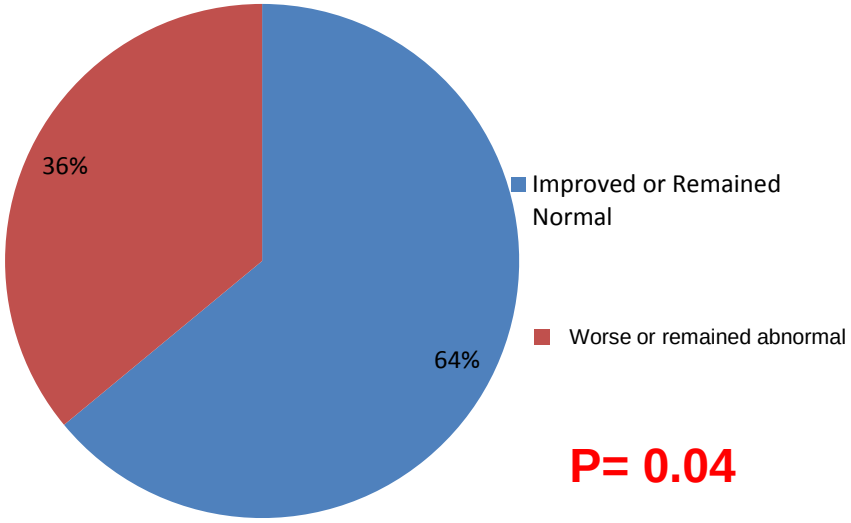
Valganciclovir (VGCV):

- L-valyl ester prodrug of ganciclovir
- Blocks viral replication
- After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases
- FDA approved to prevent CMV disease for pediatric patients receiving heart or kidney transplants
- Not FDA approved for treatment of cCMV



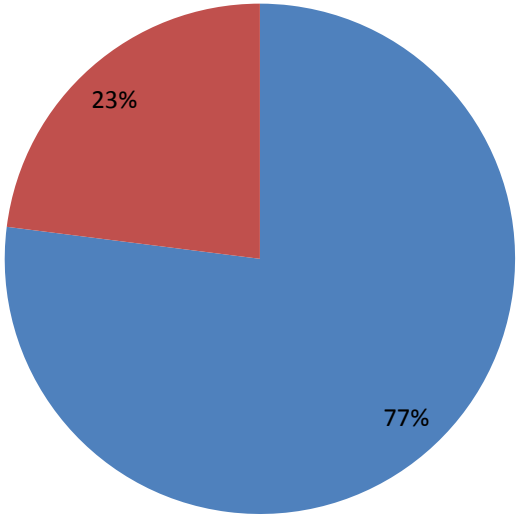
6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ Two year Followup

6 Weeks of Treatment



P= 0.04

6 Months of Treatment



Kimberlin et al. NEJM 2015

6 Weeks vs. 6 Months Valganciclovir Bayley III Outcomes 24 mo.

	6 Week Therapy	6 Month Therapy	Adjusted P-value
Cognitive Composite	76.0±2.6	84.4±2.6	0.0236
Language Composite	72.5±2.9	84.6±2.9	**0.0037**
Receptive Communication Scale	5.2±0.5	7.3±0.5	**0.0027**
Expressive Communication Scale	5.5±0.5	7.3±0.5	0.0158
Motor Composite	74.1±3.2	85.5±3.3	0.0130
Fine Motor Scale	6.4±0.6	8.0±0.6	0.0566
Gross Motor Scale	5.3±0.5	7.0±0.5	0.0198

P-values < 0.0071 (=0.05/7) considered statistically significant using Bonferroni adjustment for mutliple testing

Outcomes HT-CMV Screening for Detecting sCMV Kids (Utah):

- Two years following implementation
- 5 sCMV infants diagnosed
- Would not have been diagnosed otherwise

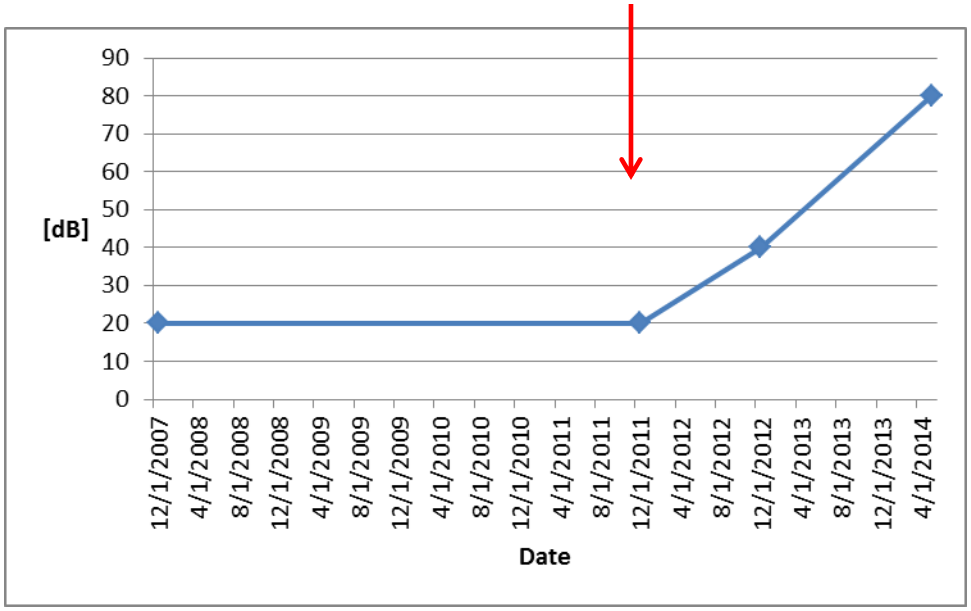
Focusing Attention on CHIP and "Asymptomatic" at Risk for Progressive Hearing Loss:

- cCMV infected hearing impaired > 50% risk for progressive hearing loss
- "Asymptomatic" cCMV infected infants have a 4 fold greater risk for hearing loss than uninfected controls
- Identification of CHIP or asymptomatic CMV kids enables us to focus attention

Lanzieri T et al. Hearing Loss in Children with Asymptomatic Congenital Cytomegalovirus Infection. Pediatrics 2017; 139(3).

Focusing on CHIP or "Asymptomatic" Infants:

- Example of Tracking hearing thresholds in a CMV infected child:

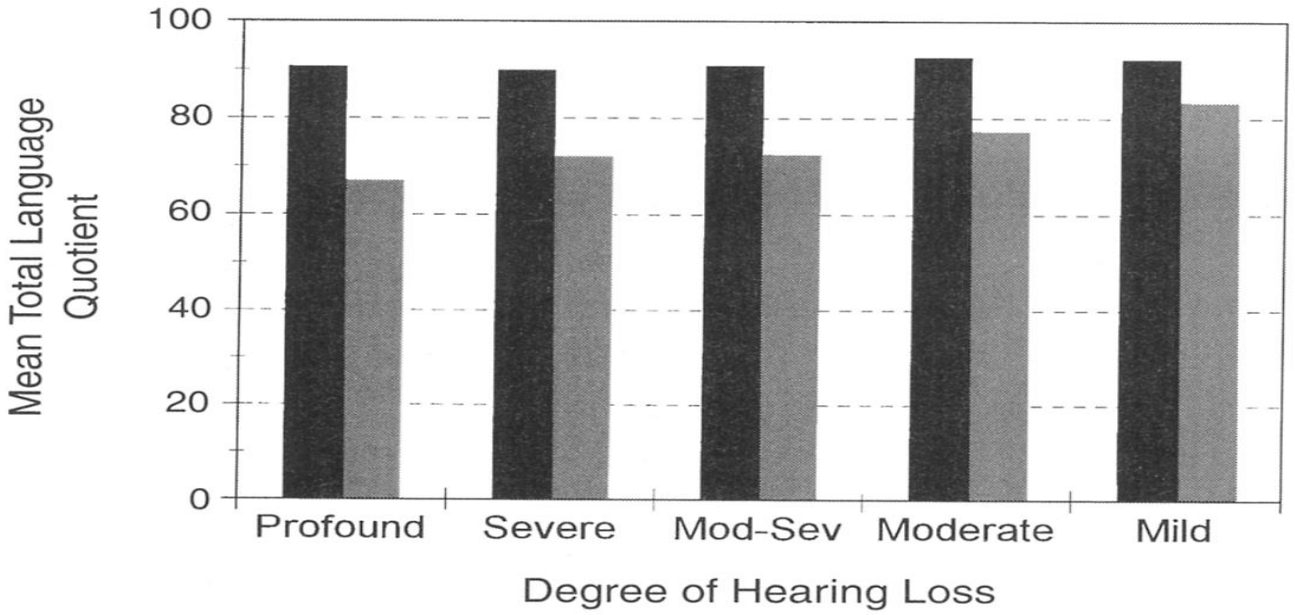


Impact HT-CMV Testing on Diagnostic Hearing Testing:

- Timely diagnostic hearing evaluation **56**% (2 years prior) and **77**% (2 years after law)!
- After the law, **86.6%** diagnostic hearing evaluation among CMV screened vs **61.5%** diagnostic hearing testing among non-CMV screened group
- **HT-CMV benefits not just CMV infected but ALL children who fail their newborn hearing screen**

Diener M et al. Outcomes From a Hearing-Targeted Cytomegalovirus Screening Program. Pediatrics. 2017.

Importance of Early Identification:



Average total language quotient for children with normal cognition by category of hearing loss and age of identification. solid bars= by 6 mo; shaded= after 6 mo.

Yoshinaga-Itano et al. Pediatrics 1998

National Survey of Newborn Hearing Screening Programs:

TABLE 1 Summary of Outcome Measures Reported by UNHSI Programs

Outcome Measure	Weighted % (Range)[a]
Newborns screened before discharge	92 (25–100)
Newborns who did not pass screening before discharge	4 (1–34)
Newborns who were referred for a diagnostic evaluation[b]	2 (1–7)
Infants who needed a diagnostic evaluation and received one	62 (15–95)
Infants who needed a diagnostic evaluation and received one by the age of 3 mo	**52 (5–93)**
Infants who did not pass the hearing screening who had a medical home	80 (5–100)
Infants with confirmed hearing loss linked to EI[b]	68 (10–100)
Infants with confirmed hearing loss linked to family-to-family support[c]	40 (5–100)

[a] States and territories reported estimated percentages, which are weighted by the number of live births reported by the state or territory. States did not report estimates for all measures.

[b] This measure reflects the percentage of infants referred for diagnostic evaluation as a result of nonpass results in the hospital before discharge or nonpass results at an outpatient rescreening.

[c] Some programs reported rates that reflect the percentage of children referred to EI or family-to-family support, whereas others reported rates that reflect the percentage of children who received services through EI or family-to-family programs. When both rates were reported, we recorded the percentage that received services.

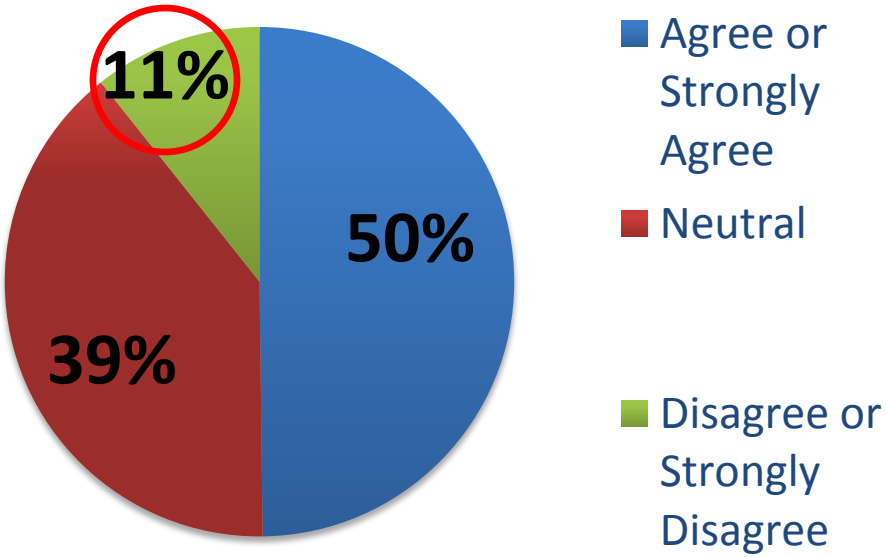
Shulman S et al. Evaluation of Universal Newborn Hearing Screening and Intervention Programs. Pediatrics 2010; 126: S19.

Utah Survey of Parental Awareness and Knowledge AFTER Utah CMV Law

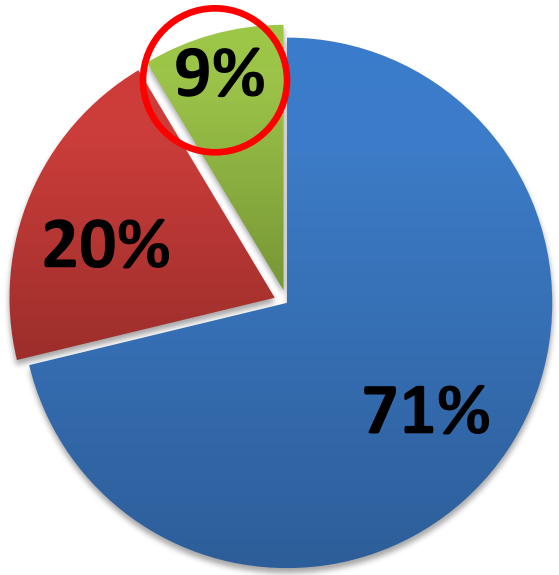
- n= 356 parents in ENT clinic
- M:F 53%:47%
- Mean age child 27 months (2 weeks to 18 years)
- 65% children -24 months or younger

Attitudes about CMV Screening

“Would want to have my baby tested even if my doctor/hospital didn't do it routinely”

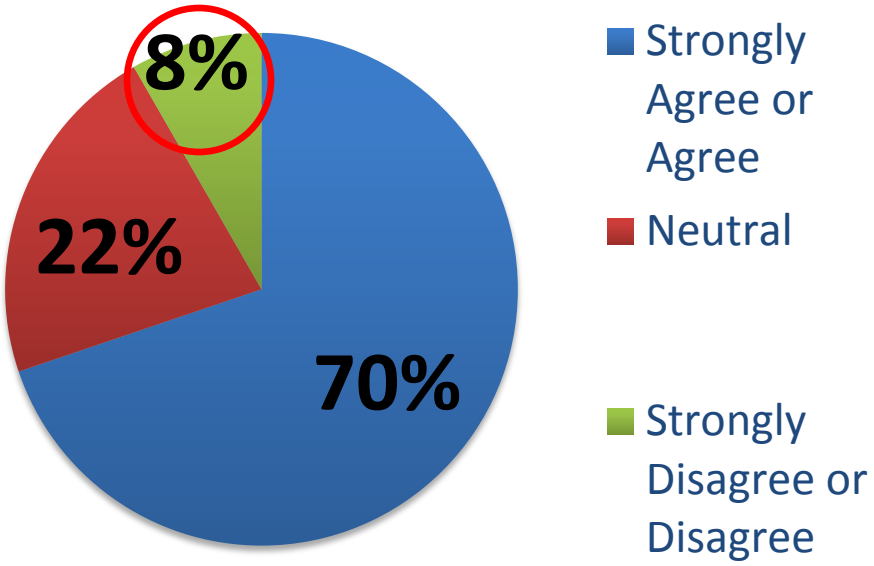


"Would want to know if my child has CMV even if he or she never develops problems

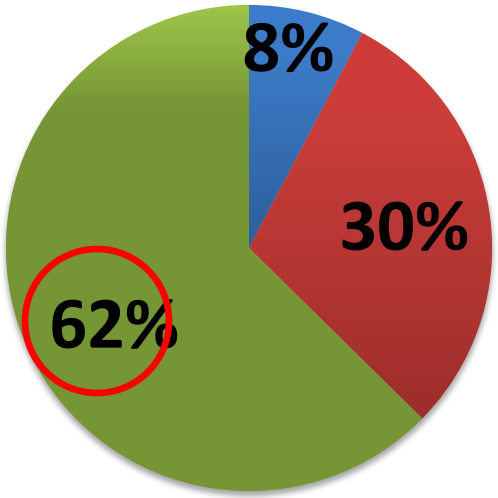


Attitudes about CMV Screening

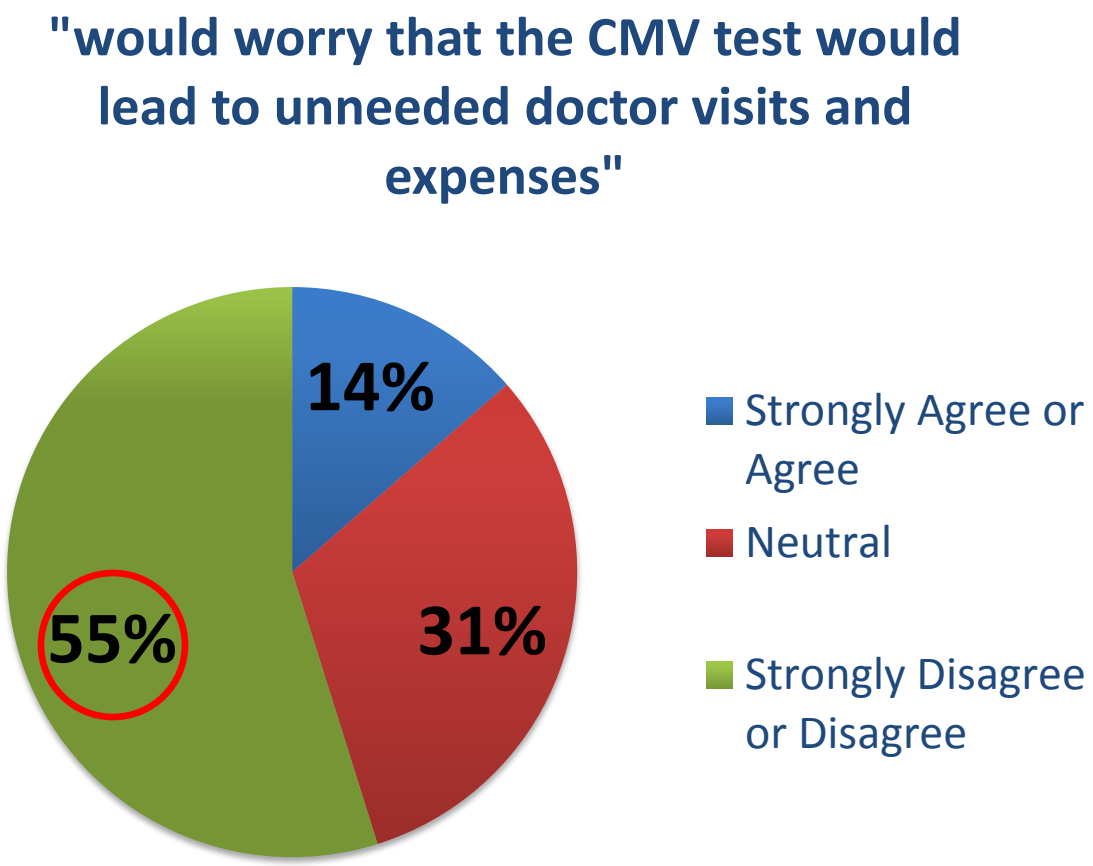
"Would be willing to pay $20 to have my baby tested for CMV"



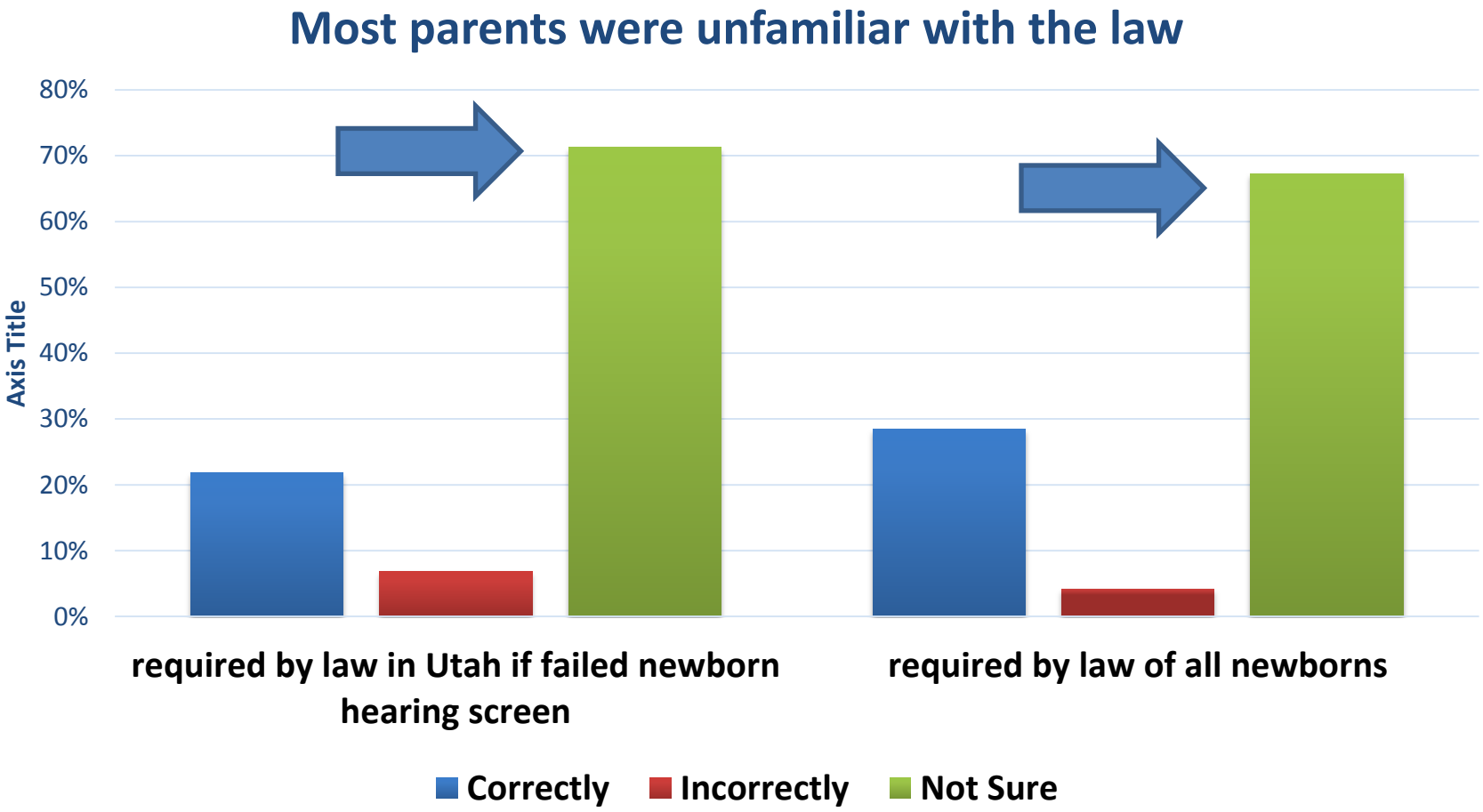
"Would be more worried about the stigma associated with a CMV diagnosis than about the health effects of CMV"



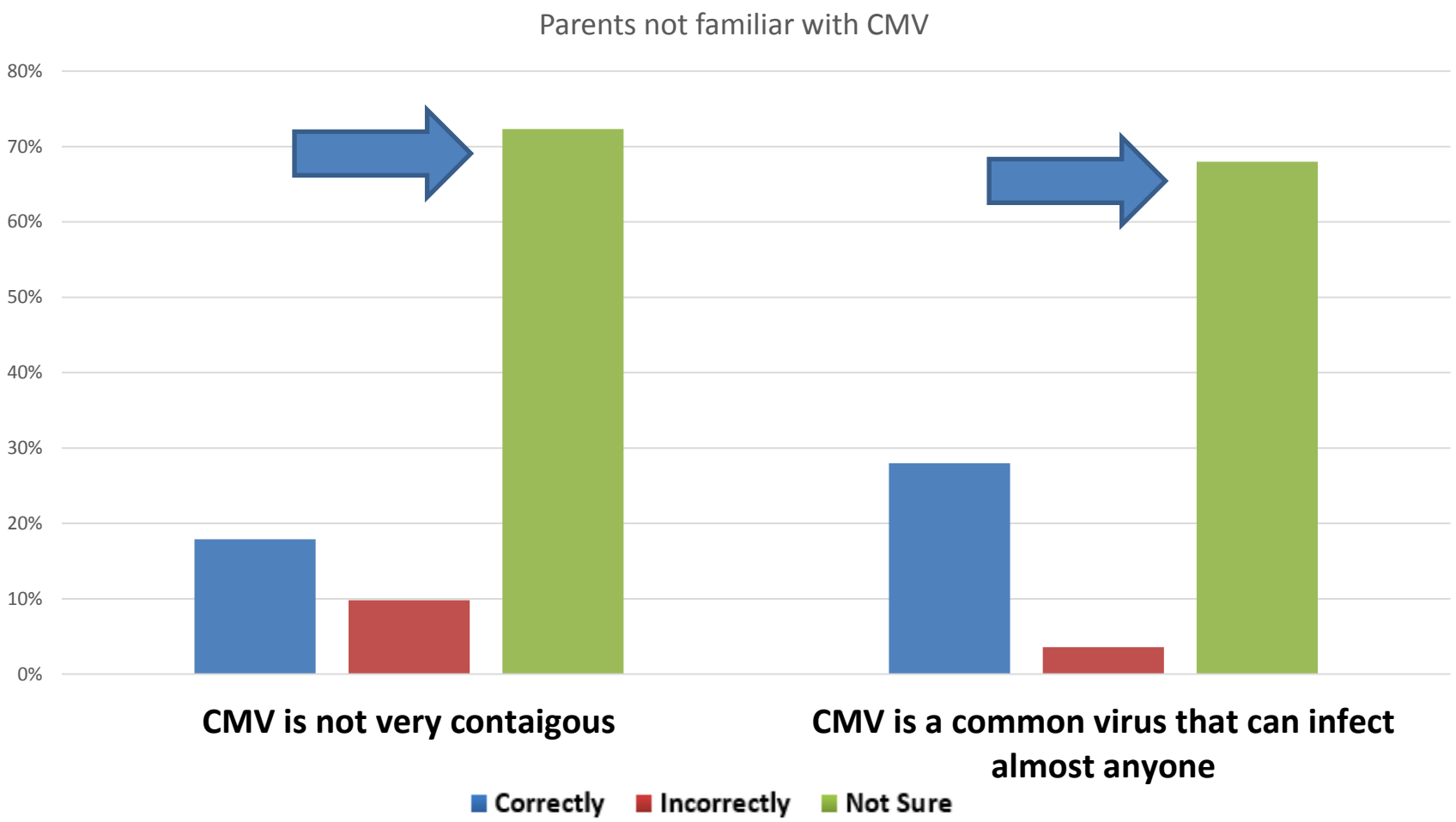
Attitudes about CMV Screening



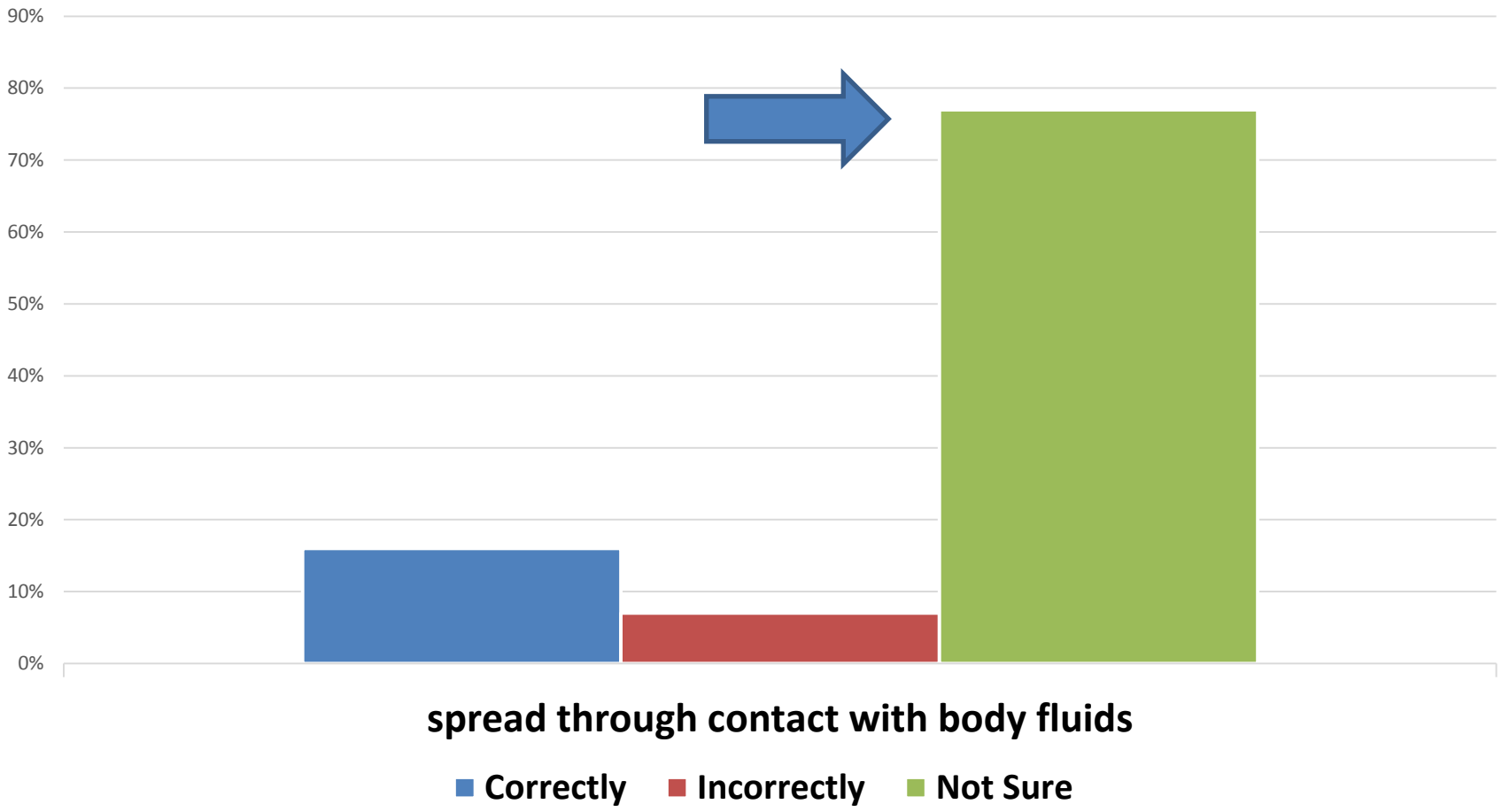
Parents' Knowledge of CMV Law



Parents' Knowledge of CMV



Parents' Knowledge of CMV



What about Antiviral Therapy of CHIP?

- 26 day old infant presented with CMV induced SNHL
- Failed NBHS
- Saliva CMV PCR @ 3 wks age- positive
- ABR- normal right and left profound SNHL
- Ophthalmology exam- normal
- HUS-normal

Rationale for Antiviral Therapy for CHIP:

- VGC x 6 weeks
- FU audio 2+ yrs after rx- stable hearing
- Speech progressing normally

The Controversy with VGCV for CHIP:

"Antiviral therapy is **not** the standard of care of infants with cCMV infection who have isolated SNHL as there are insufficient data to support the safety or efficacy of treating these infants.."

Joseph Bocchini, Jr., M.D.
Professor and Chairman
Department of Pediatrics, LSU

NIH Valganciclovir Ear Trial:

- **Aim 1: Compare the hearing and language outcomes of cCMV-infected with isolated hearing loss treated with VGCV to untreated infants via a multi-institutional double-blinded placebo controlled clinical trial.**

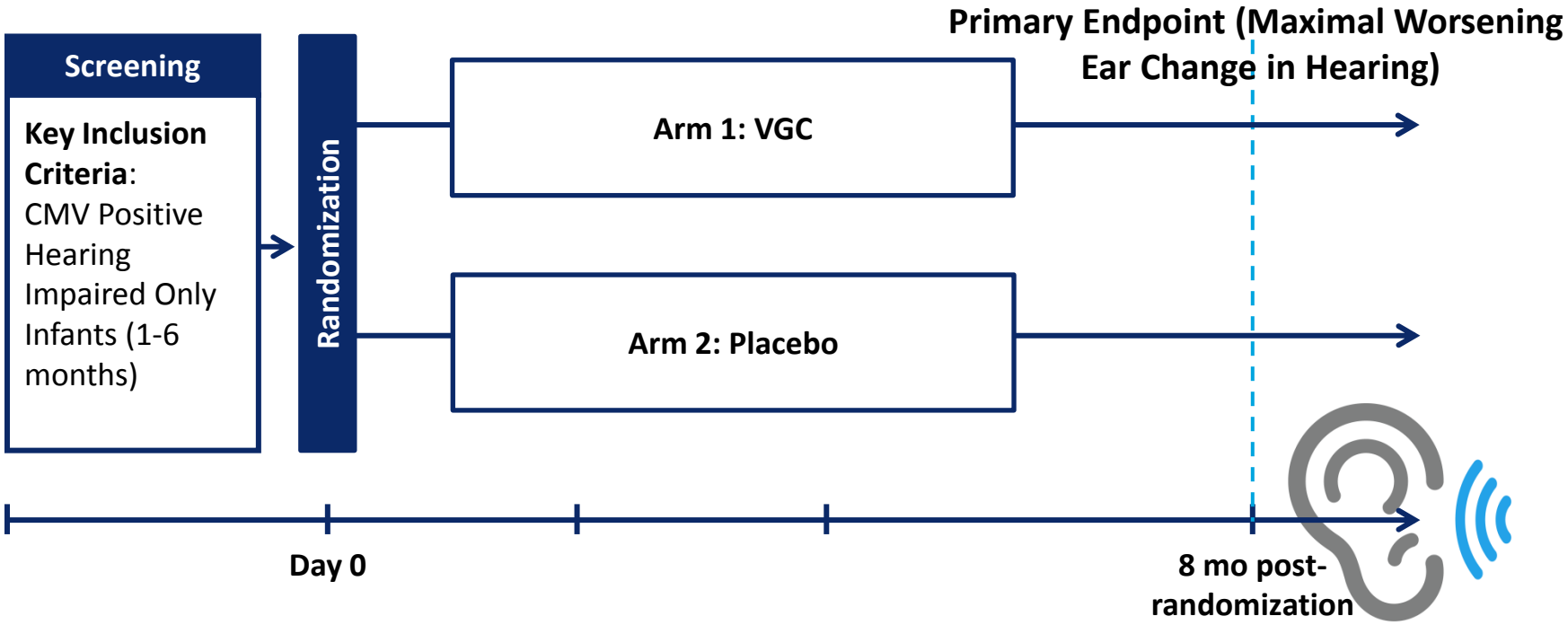
- **Aim 2: To evaluate the safety of antiviral VGCV therapy for cCMV-infected infants with isolated hearing loss.**

- **Aim 3. Evaluate the pharmacokinetics of valganciclovir using pharmacometric modeling to develop a population pK model.**

ValEAR Trial
a CMV Study

Study Design:

cCMV Hearing Impaired Only (CHIP) Infants Randomized to Valganciclovir (VGC) or Placebo



ValEAR Trial
a CMV Study

Current Status:

- FDA approved May 2017
- UU IRB approved May 2017
- NIDCD- LOA July 2017 as U01
- Genetech- subcontract Nov. 2017
- Budget approved by NIDCD Feb 2018
- Training June 2018
- Sites contracts -finalizing
- Enrollment- soon

ValEAR Trial
a CMV Study

Over Thirty Institutions Starting HT-CMV Screening!

ValEAR Trial
a CMV Study

Take Home Message:

- "~~No~~ There is evidence … supports "treatment" of newborns who test positive for CMV but are otherwise asymptomatic…including those w HL"

a. Provides providers and parents etiology for SNHL
b. Increases opportunity to dx Sx cCMV patient
c. Focus at risk patients (asymptomatic or CHIP) for progressive loss
d. Improves time to diagnose hearing loss for **ALL** infants who failed their newborn hearing screen
e. Role of antiviral rx- pending (ValEAR Trial)

Practice Patterns	Number	%
Do you incorporate any type of cCMV testing for children with SNHL?		
Always	8	11%
Sometimes	22	31%
Rarely	20	29%
Never	20	29%
Do you offer DBS CMV PCR testing for your patients?		
Yes	16	23%
No	52	76%
Do you offer antiviral therapy or refer to infectious disease specialist for antiviral therapy for cCMV infected children?		
Yes, only if they are symptomatic	15	21%
Yes, for symptomatic children and asymptomatic children that fail the hearing screen	28	40%
No	12	17%
I don't know	15	21%

Hearing Targeted Early CMV Screening :

The Laryngoscope

The Triological Society
Best Practice

Should Infants Who Fail Their Newborn Hearing Screen Undergo Cytomegalovirus Testing?

Albert H. Park, MD; Angela Shoup, PhD

BEST PRACTICE

Given the current evidence available, it is recommended that infants who fail their newborn hearing screening should undergo CMV testing.

Park AH, Shoup A, Laryngoscope. 2017 Aug 16. doi: 10.1002/lary.26819. [Epub ahead of print]

Screening all Newborns in California?

- Universal almost 500,000 vs HT-CMV 5000 annually in California
- Logistical challenge- personnel costs, transport, laboratory infrastructure, insurance coverage
- Educating parents/personnel- approx. 85% asymptomatic

What About Universal CMV Screening?

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

William D Rawlinson, Suresh B Boppana, Karen B Fowler, David W Kimberlin, Tiziana Lazzarotto, Sophie Alain, Kate Daly, Sara Doutré, Laura Gibson, Michelle L Giles, Janelle Greenlee, Stuart T Hamilton, Gail J Harrison, Lisa Hui, Cheryl A Jones, Pamela Palasanthiran, Mark R Schleiss, Antonia W Shand, Wendy J van Zuylen

The group recommended that consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants, facilitating early detection and intervention for sensorineural hearing loss

Rawlinson W et al. Lancet Infect Dis. 2017 S1473-3099 (17) 30143-3.

Universal cCMV vs HT-CMV Approaches:

- Ontario using universal DBS cCMV screening as standard of care
- Several states and multiple institutions implementing HT-CMV
- Cost and logistics
- “Normal” cCMV infants difficult to manage-one-third in HT-CMV cohort

Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening

Karen B. Fowler, DrPH,[a] Faye P. McCollister, EdD,[b] Diane L. Sabo, PhD,[c] Angela G. Shoup, PhD,[d]
Kris E. Owen, AuD,[d] Julie L. Woodruff, AuD,[e] Edith Cox, AuD,[f] Lisa S. Mohamed, AuD,[f]
Daniel I. Choo, MD,[g] Suresh B. Boppana, MD,[h] on behalf of the CHIMES Study

Fowler et al. Pediatrics 2017

Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

- NBHS identified 57% infants who had CMV-related SNHL in newborn period
- 43% cCMV infants not identified via HT-CMV
- Used saliva for cCMV screening
- Newborn hearing screening methodology not presented
- Not clear methodology diagnostic ABR testing
- Need validation of newborns diagnosed with ABR testing with behavioral testing

Fowler et al. Pediatrics 2017

Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

- 4/178 cCMV from HT-CMV with hearing loss- no significant difference from those identified from universal screening (Roth et al. Arch Dis Child Fetal Neonatal Ed 2017)
- 11,861 Brazilian newborns universal CMV screening AND hearing screening- 8 diagnosed with cCMV and SNHL. HT-CMV screening detected 7/8. No later onset of progressive SNHL FU 18 mo (Yamamoto et al. CMV Public Policy Meeting, 2018)

Cost Effectiveness of Early CMV Screening:

JAMA Pediatrics | Original Investigation

Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection

Soren Gantt, MD, PhD, MPH; Francois Dionne, PhD; Fred K. Kozak, MD; Oran Goshen, MD; David M. Goldfarb, MD; Albert H. Park, MD; Suresh B. Boppana, MD; Karen Fowler, DrPH

Cost Effectiveness Universal or HT-CMV Approaches:

Table 4. Estimated Mean Incremental Costs per Newborn to Identify Cases of cCMV Infection and Related Hearing Loss

	Screening Strategy, $[a]			
	Universal		Targeted	
Cost	10/Test	50/Test	10/Test	50/Test
Cost to identify 1 cCMV infection	2000	10 000	566	2832
Cost to identify 1 cCMV-related hearing loss	27 460	90 038	975	3916
Cost to prevent 1 cochlear implant[b]	4 064 157	12 620 277	39 401	271 947

Abbreviation: cCMV, congenital cytomegalovirus.

[a] All costs are in 2016 US dollars.

[b] Assumes valganciclovir hydrochloride treatment of only symptomatic newborns, calculated as the number of newborns who needed to be screened to prevent 1 cochlear implant case multiplied by the incremental cost of screening, follow-up, and valganciclovir per newborn screened.

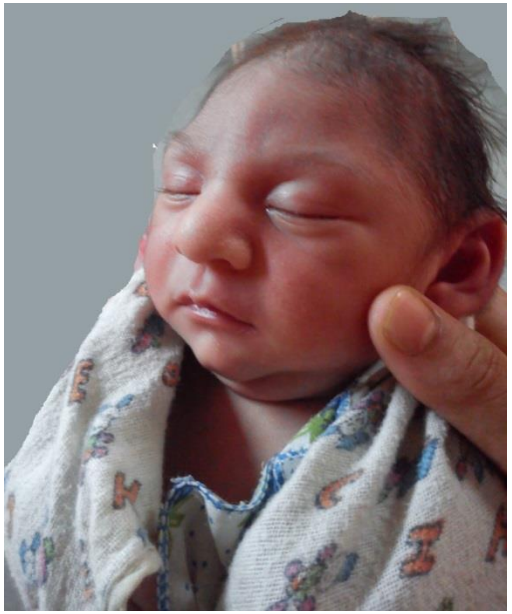
Gantt et al. JAMA Pediatrics 2017

	None	Selective	Universal
Costs (2001 US dollars)			
Total cost of detection of deafness in cohort†	$69 200	$671 200	$2 122 700
Cost per infant whose deafness is diagnosed by 6 mo	$2300	$10 100	$21 400
Lifetime costs of all care related to deafness and lost productivity	$116 980 800	$115 520 600	$114 648 300
Cost per deaf child with normal language outcomes	$2 215 500	$1 978 100	$1 769 300
Incremental cost or saving (2001 US dollars)			
Incremental cost per infant whose deafness is diagnosed 6 mo‡	-	$16 400	$44 300
Incremental total savings over lifetime of deaf cohort‡	-	$1 460 200	$872 300

Keren et al. Pediatrics 2002

What About Targeted Screening Beyond Just Hearing Screening?

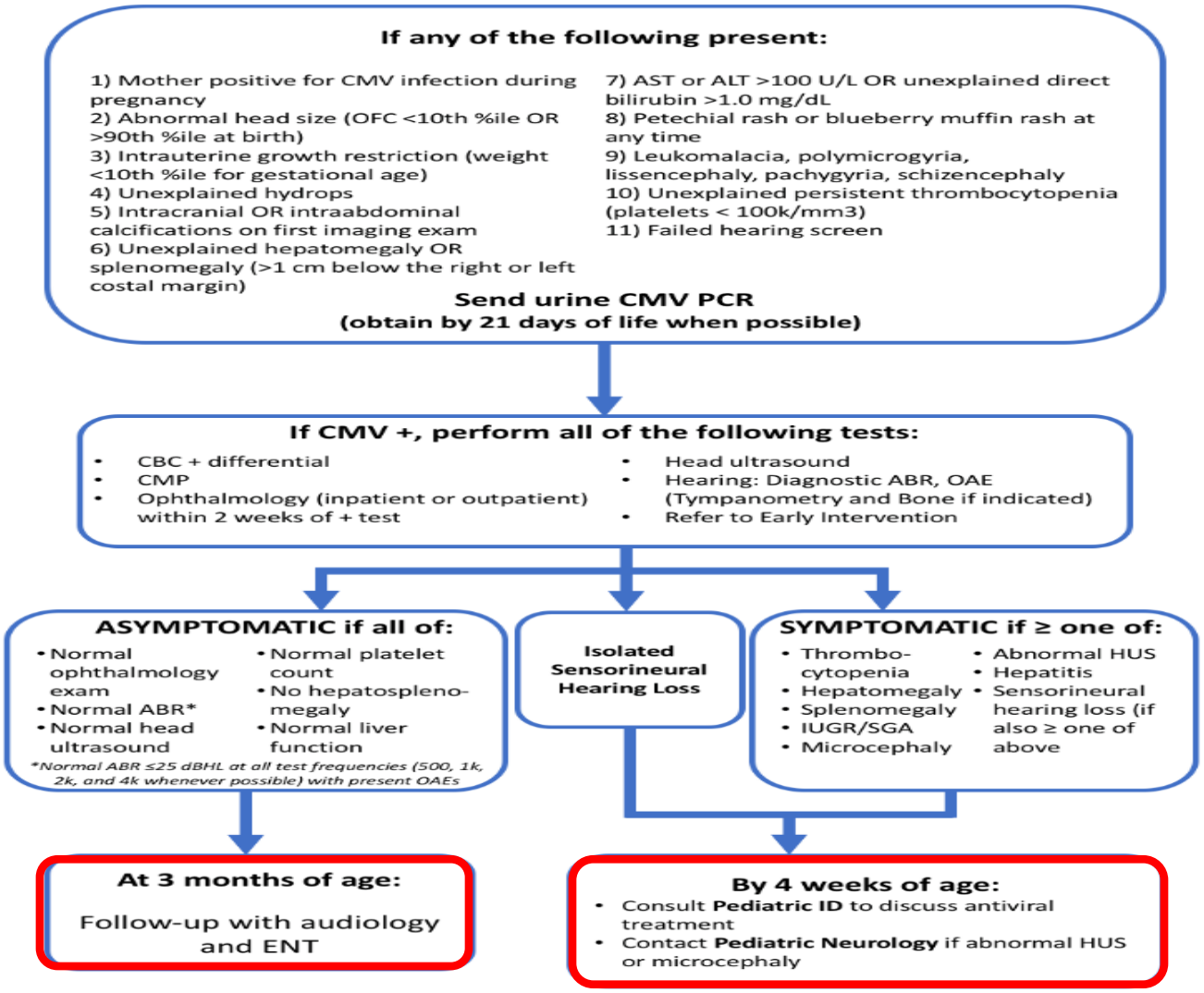
- Benefit from antiviral
- N=349 patients
- Targeted Screening
- 19/349 (5.4%) cCMV +
- IUGR (47.1%)
- NBHS fail (11.8%)
- Thrombocytopenia (11.8%)



What Can You Do?

- Start HT-CMV and NICU/newborn testing
- Talk to your Colleagues, Audiologists, Pediatricians and Newborn Medical Directors
- Almost 100 hospitals performing HT-CMV testing
- Implement DBS CMV PCR testing
- Every state has DBS that can be tested for CMV

What about Surveillance?



Hearing Surveillance?

- How frequent and for how long?

Asymptomatic- if no hearing loss by age 5 yrs no greater risk for progressive hearing loss later compared to uninfected controls

CHIP- progressive HL continues thru 18 yrs

Lanzieri et al. Pediatrics 2017

CHIP Hearing Surveillance?

- Best or worse ear? Worse ear thru 1st yr

Fraction develop worsening hearing in the better ear and no change in worse ear. 0/8

Fraction develop worsening hearing in the worse ear and no change in best ear. 5/8

Fraction develop worsening in both ears 1/8

Fraction develop no change in either ear 1/8

Fraction develop improvement in either ear 1/8

- Worse ear tends to worsen more frequently than better ear

Torrecillas, Lanzieri, Demmler, et al. pending

Hearing Surveillance?

- Which frequencies are most likely to worsen?
- 1,2,4k Hz over 18 years
- No specific frequency

Torrecillas, Lanzieri, Demmler, et al.
pending

Hearing Surveillance?

- Do symptomatic, asymptomatic or CHIP behave differently? Yes

McCrary et al. Int J Peds Oto. In press

Hearing Surveillance

- N=16 sCMV all underwent VGC treatment
- 14/16 clinically worsening hearing
- Worse vs better ear (n=11)

No change (2/11)

Both ears worse (3/11)

Better ear worse (3/11)

Worse ear worse (3/11)

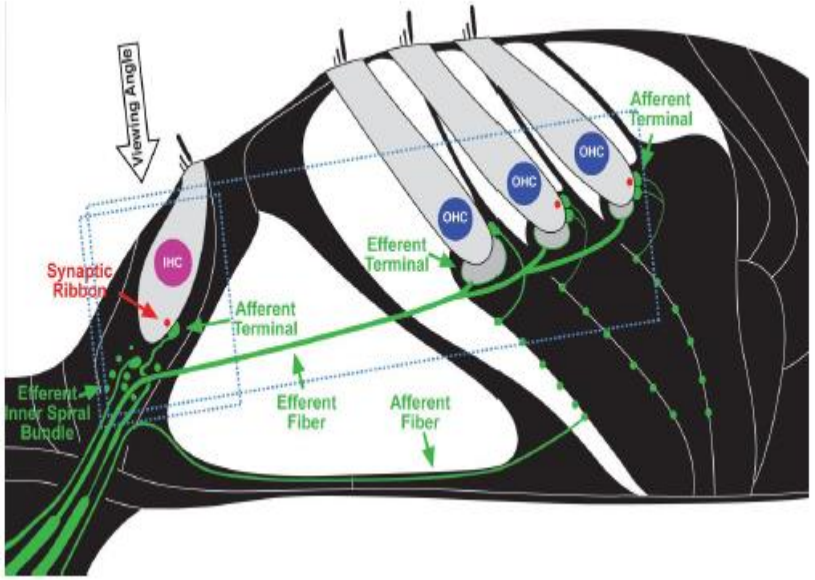
McCrary et el. Int J Peds Oto in press

Recommendations for Hearing Surveillance:

- Evolving
- Risk higher with CHIP, sCMV infected
- Every 3 months x 3 years then every 6 months through 18 years
- **Both ears need to be tested**

Future Directions:

- Loss of synaptic connections of the spiral ganglion cells without elevated audiometric thresholds
- Studied age and noise induced SNHL
- Can a similar effect be seen in CMV?



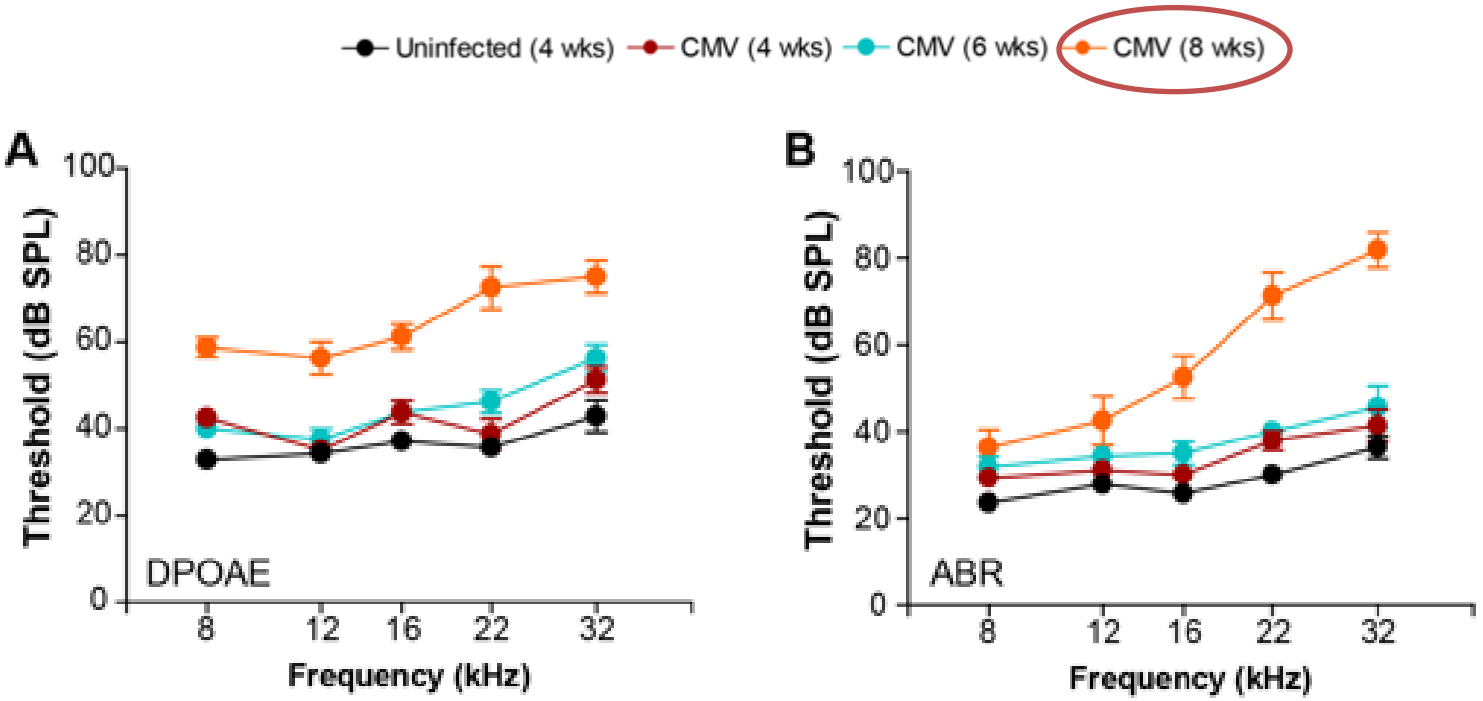
Kujawa and Liberman 2008

Study Design:

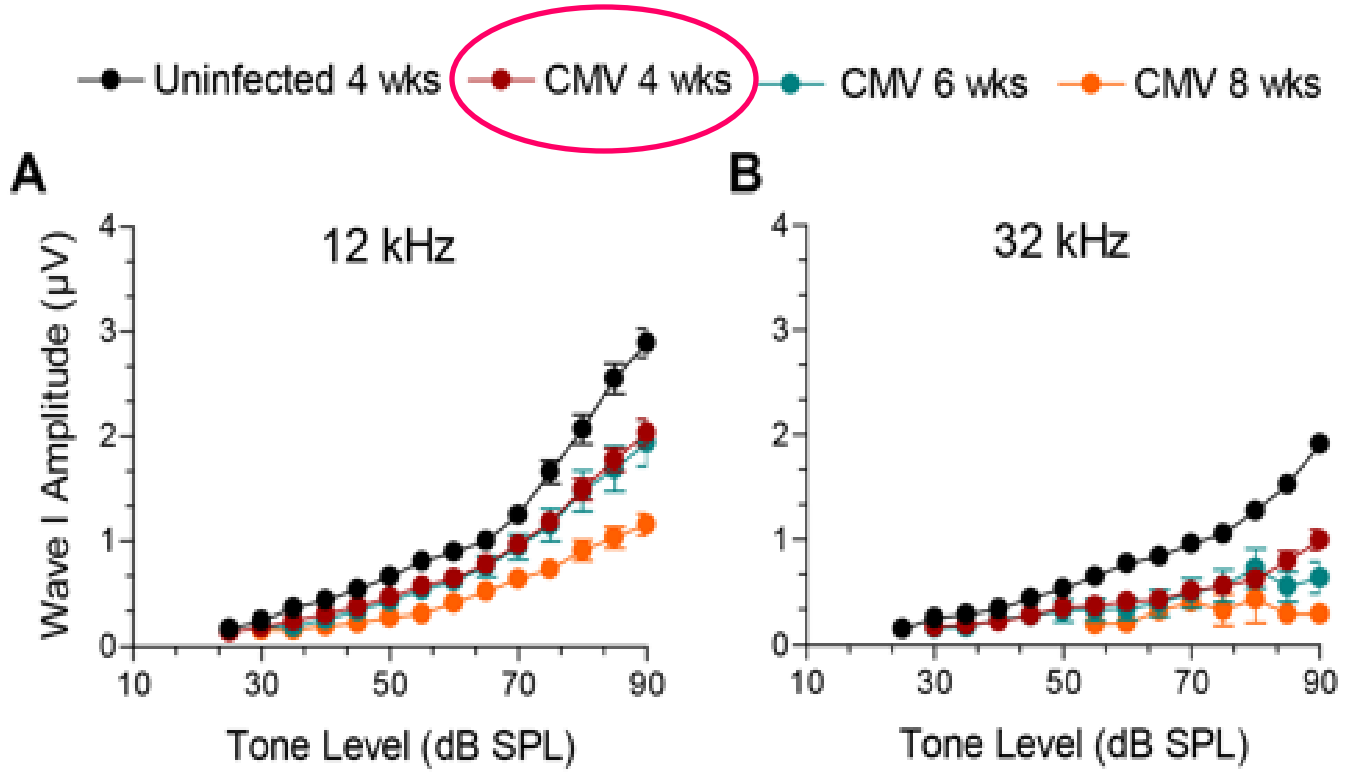
P3 days old
IC injection
mCMV 200 pfu
C57BL/6

ABR thresholds,
Amplitude and
Ribbon synapse
Counts
4,6 and 8 weeks

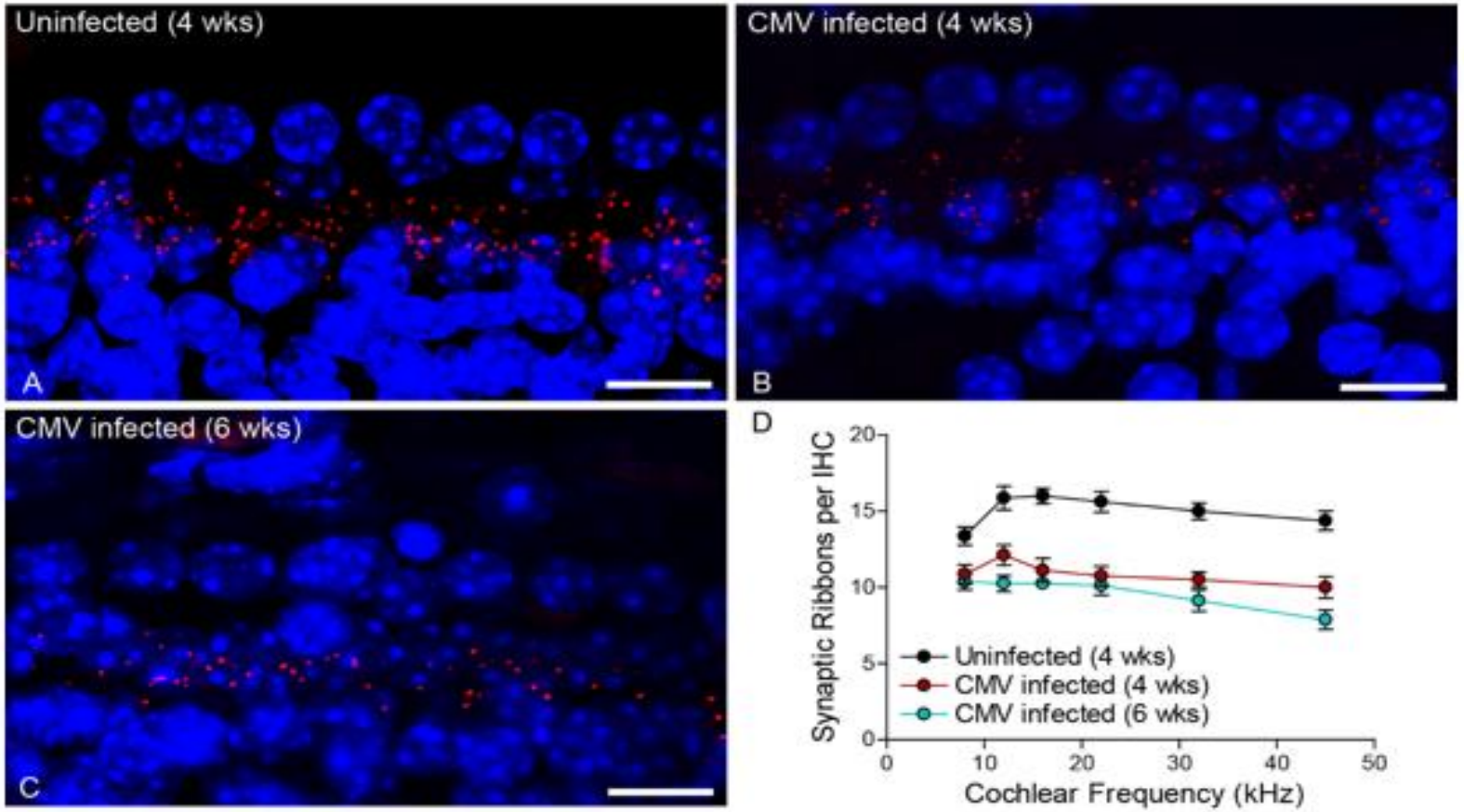
ABR Thresholds:



Suprathreshold Responses:



Ribbon Synapse Counts:



Summary:

- Synaptopathy occurs in murine model for CMV
- Does this occur in children with CMV?

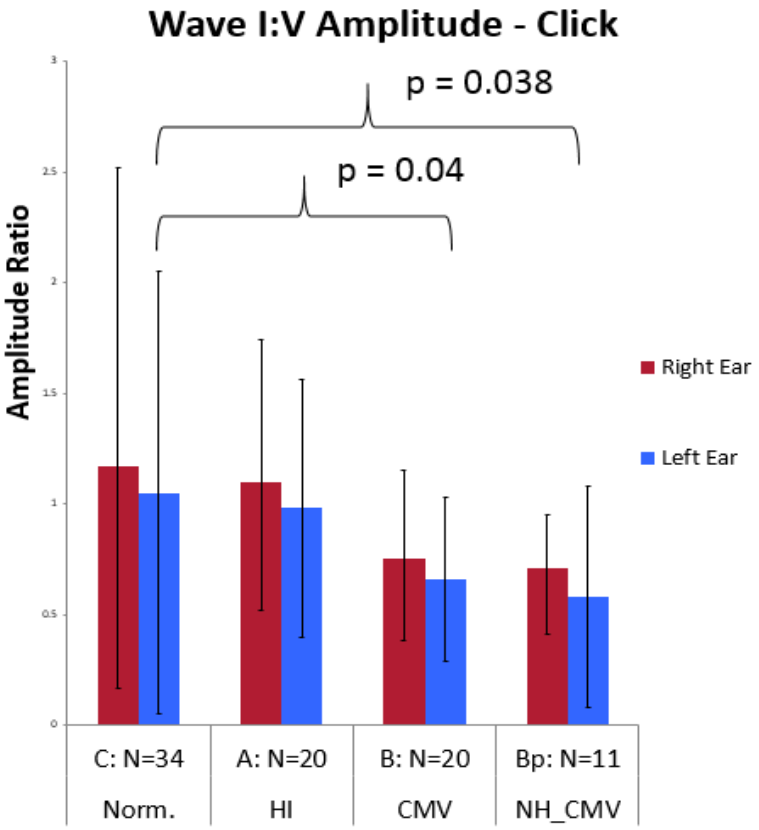
Clinical Study:

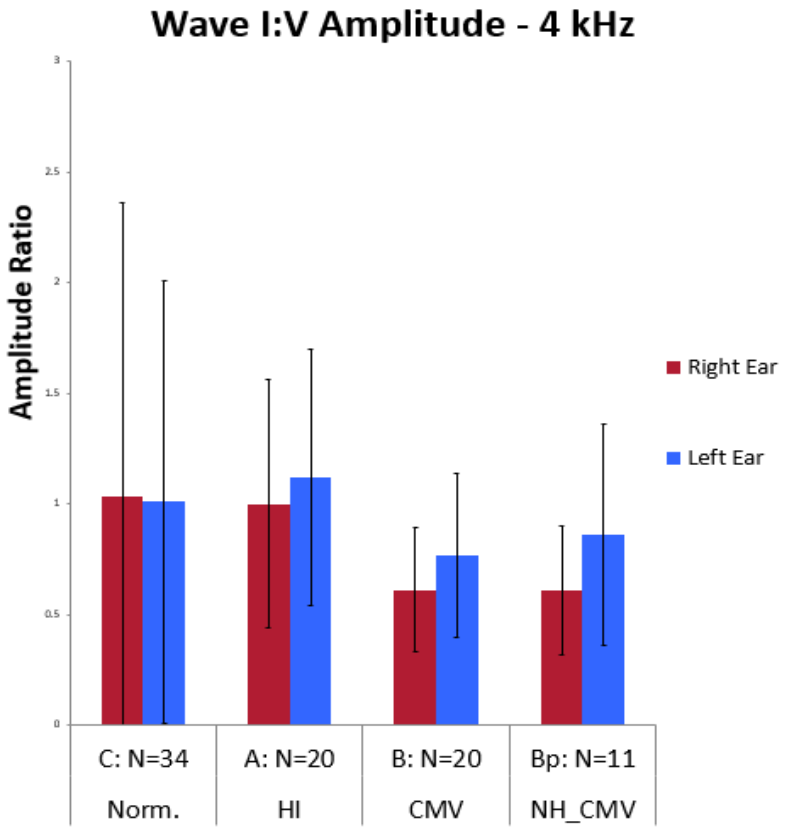
- A retrospective study design
- 4 groups: hearing impaired (HI) patients without CM and with cCMV, and normal hearing patients with and without cCMV (A, B, B’ and C respectively)
- Ages of 14 days - 17 years who obtained ABRs at Primary Children’s Hospital between 2014-2018
- ABR waveforms -Integrity Vivisonic ABR equipment
- ABRs (45-90 dB nHL) using click and 4 kHz toneburst stimuli
- Outcomes used for analysis: I/V amplitude ratio
- The following additional data was taken into consideration when analyzing data: intensity, rate, polarity, gender and patient chronological age

Patient Demographics:

	Group A HI without cCMV	Group B cCMV Positive	Group B' cCMV with normal hearing	Group C Normal Hearing
Age (standard deviation)	21.9 months (35.34)	14.37 months (13.48)	14.75 months (14.29)	22.45 months (35.34)
Gender (Male/Female)	10/10	7/13	4/7	20/14
Intensity (click) Right/Left dB nHL	80.79/78	75.56/67.63	73.57/62.5	67.35/65.61
Intensity (4kHz) Right/Left dB nHL	77.89/77.89	62.81/60	55.71/52.86	61.92/60.45

Wave I Amplitude Reduced in cCMV infected children (click):





Summary:

- Synaptopathy may occur in cCMV infected children
- Limitations- retrospective, not all underwent suprathreshold stimuli
- Need prospective study
- Implications- help identify cCMV children postnatally

Conclusion:

- Convince you that CMV is an important topic
- Awareness low- caregivers AND providers
- Rationale for targeted screening but not universal
- ValEAR trial – role of universal or targeted screening
- What steps you can do
- Future research needed

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Training session at Salt Lake City June 6, 2018

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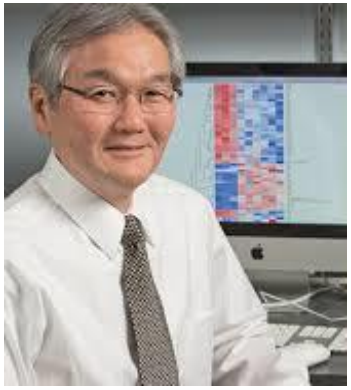

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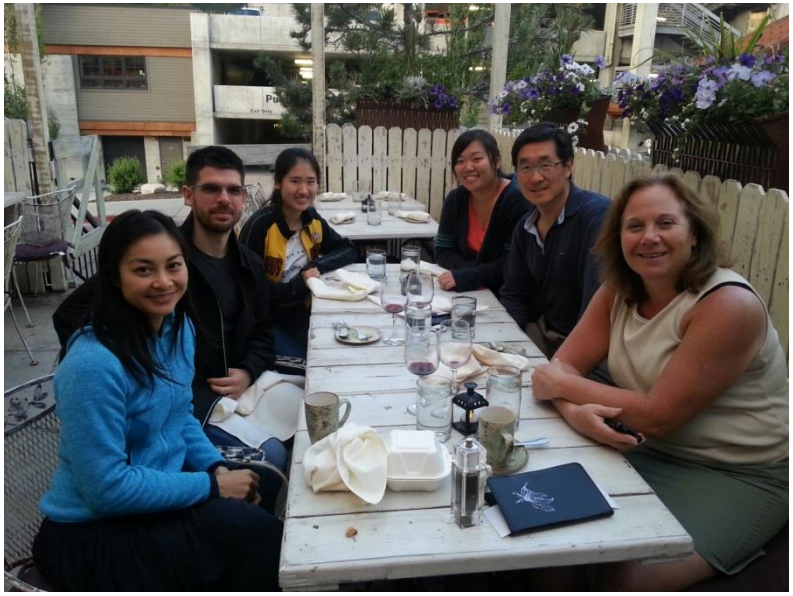

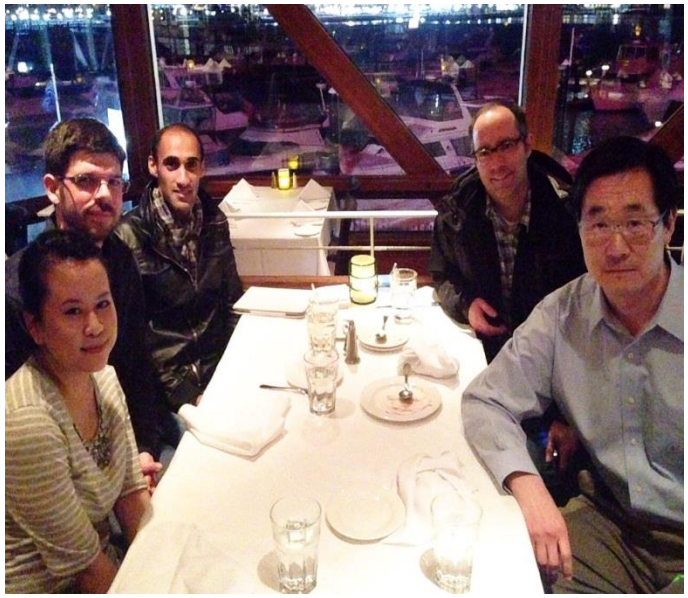

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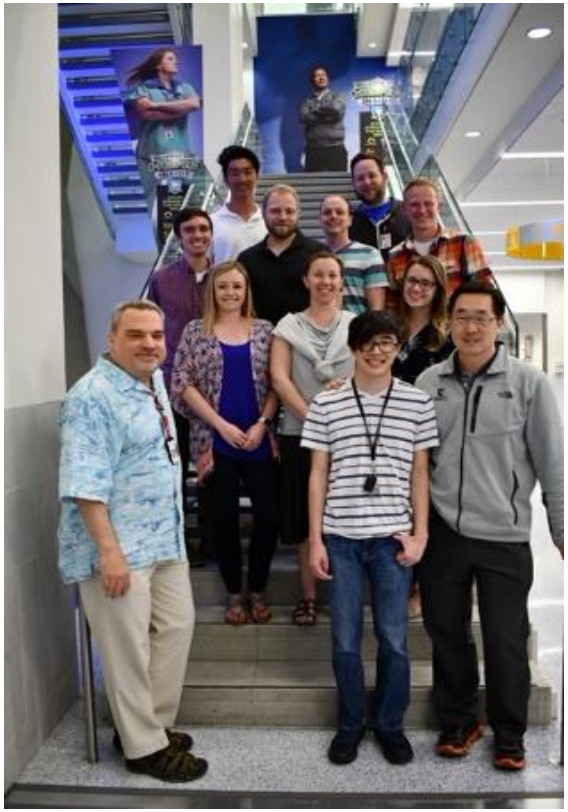

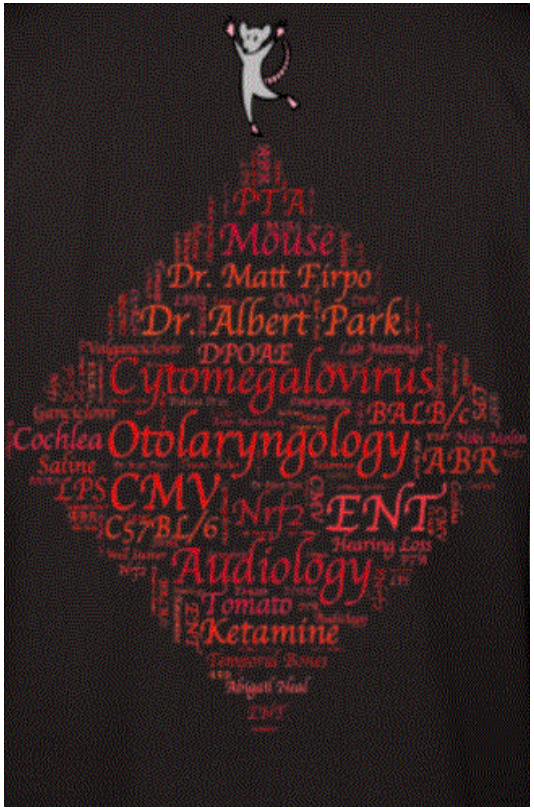

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