The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

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Nondisclosure:

- Triological Career Development Award- murine model of CMV induced SNHL
- Industry supported grant (Otonomy)
- Multiinstitutional study CYP2D6 adenotonsillectomy clinical trial
- None of these grant relevant to this presentation

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

Objectives:

- CMV induced SNHL not recognized in literature
- If you look for CMV in these patients, you will find it often
- There are compelling reasons for early CMV diagnosis
- The advantages of the Utah CMV law
- The limitations of the law

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

“Progress is impossible without change, and those who cannot change their minds cannot change anything.”

George Bernard Shaw

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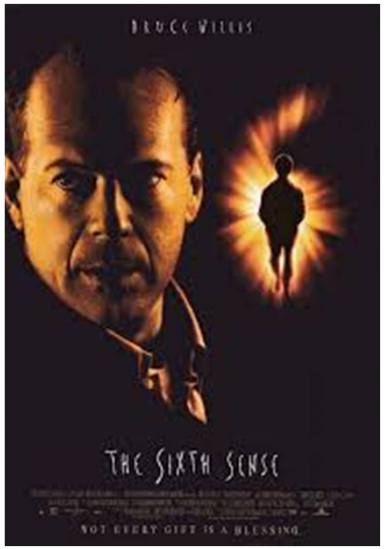
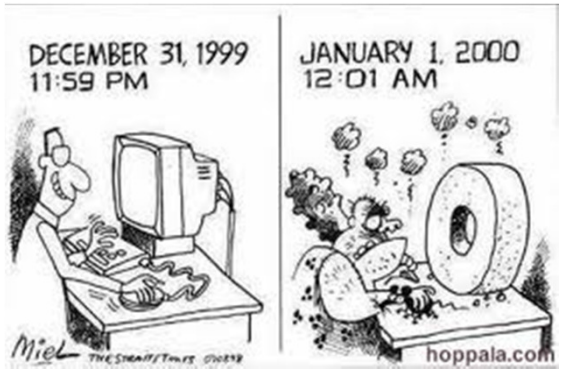
Events in 1999:





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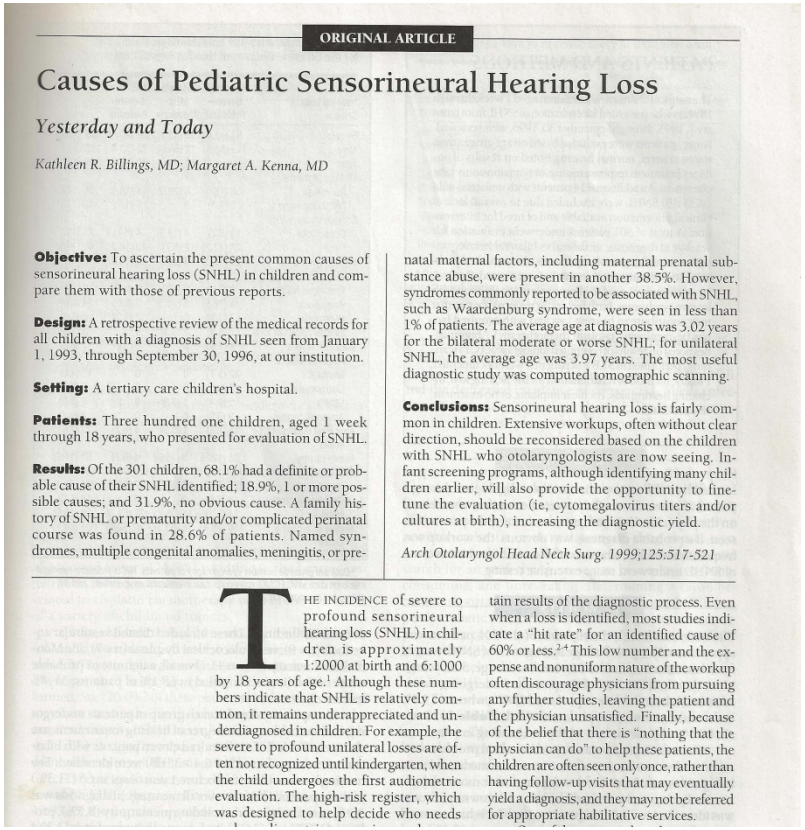
Billings and Kenna. Arch. OHNS 1999



ORIGINAL ARTICLE

Causes of Pediatric Sensorineural Hearing Loss

Yesterday and Today

Kathleen R. Billings, MD; Margaret A. Kenna, MD

Objective: To ascertain the present common causes of sensorineural hearing loss (SNHL) in children and compare them with those of previous reports.

Design: A retrospective review of the medical records for all children with a diagnosis of SNHL seen from January 1, 1993, through September 30, 1996, at our institution.

Setting: A tertiary care children's hospital.

Patients: Three hundred one children, aged 1 week through 18 years, who presented for evaluation of SNHL.

Results: Of the 301 children, 68.1% had a definite or probable cause of their SNHL identified; 18.9%, 1 or more possible causes; and 31.9%, no obvious cause. A family history of SNHL or prematurity and/or complicated perinatal course was found in 28.6% of patients. Named syndromes, multiple congenital anomalies, meningitis, or prenatal maternal factors, including maternal prenatal substance abuse, were present in another 38.5%. However, syndromes commonly reported to be associated with SNHL, such as Waardenburg syndrome, were seen in less than 1% of patients. The average age at diagnosis was 3.02 years for the bilateral moderate or worse SNHL; for unilateral SNHL, the average age was 3.97 years. The most useful diagnostic study was computed tomographic scanning.

Conclusions: Sensorineural hearing loss is fairly common in children. Extensive workups, often without clear direction, should be reconsidered based on the children with SNHL who otolaryngologists are now seeing. Infant screening programs, although identifying many children earlier, will also provide the opportunity to fine-tune the evaluation (ie, cytomegalovirus titers and/or cultures at birth), increasing the diagnostic yield.

Arch Otolaryngol Head Neck Surg. 1999;125:517-521

THE INCIDENCE of severe to profound sensorineural hearing loss (SNHL) in children is approximately 1:2000 at birth and 6:1000 by 18 years of age.[1] Although these numbers indicate that SNHL is relatively common, it remains underappreciated and underdiagnosed in children. For example, the severe to profound unilateral losses are often not recognized until kindergarten, when the child undergoes the first audiometric evaluation. The high-risk register, which was designed to help decide who needs certain results of the diagnostic process. Even when a loss is identified, most studies indicate a "hit rate" for an identified cause of 60% or less.[2-4] This low number and the expense and nonuniform nature of the workup often discourage physicians from pursuing any further studies, leaving the patient and the physician unsatisfied. Finally, because of the belief that there is "nothing that the physician can do" to help these patients, the children are often seen only once, rather than having follow-up visits that may eventually yield a diagnosis, and they may not be referred for appropriate habilitative services.

Table 2. Epidemiologic Features of Previous Studies for Children With Bilateral Moderate to Severe SNHL*

	Reference (Year)			
Hearing Loss Criteria	Parving[6] (1983)	Pappas and Schaibly[2] (1984)	Parving[4] (1985)	Present Study (1997)
No. of children	117 (100.0)	127 (100.0)	94 (100.0)	211 (100.0)
Known cause	85 (72.6)	81 (63.8)	69 (73.4)	159 (75.4)
Unknown cause	32 (27.4)	46 (36.2)	25 (26.6)	52 (24.6)
Genetic	39 (33.3)	28 (22.0)	31 (33.0)	52 (24.6)
Family history	32 (27.4)	10 (7.9)	25 (26.6)	26 (12.3)
Syndromal	7 (6.0)	18 (14.2)	7 (7.4)	26 (12.3)
Inner ear defects	0	12 (9.4)	0	25 (11.8)
Prenatal insult	16 (13.7)	16 (12.6)	14 (14.9)	40 (19.0)
TORCH infections	19 (16.2)	25 (19.7)	17 (18.1)	3 (1.4)
Meningitis	3 (2.6)	16 (12.6)	7 (7.4)	12 (5.7)
Chronic otitis media	2 (1.7)	0	1 (1.2)	51 (24.2)

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

A diagnostic paradigm for childhood idiopathic sensorineural hearing loss

DIEGO A. PRECIADO, MD, LYNNE H.Y. LIM, MD, ALIZA P. COHEN, MA, COLM MADDEN, MD, DAVID MYER, BS, CHRIS NGO, BS, JOHN K. BRADSHAW, MD, LOUISE LAWSON, PHD, DANIEL I. CHOO, MD, and JOHN H. GREINWALD, JR, MD, Cincinnati, Ohio

OBJECTIVE: **Our objective was to determine the diagnostic yield of laboratory testing, radiological imaging, and *GJB2* mutation screening in a large cohort of patients with differing severities of idiopathic sensorineural hearing loss (SNHL).**

DESIGN AND SETTING: **We undertook a retrospective study of patients presenting with SNHL at our institution from 1993 to 2002.**

RESULTS: **Laboratory testing had an extremely low yield. Patients with unilateral SNHL had a significantly higher imaging yield than those with bilateral. The diagnostic yield of *GJB2* screening was significantly higher in patients with severe to profound SNHL than in those with less severe SNHL. However, a relatively large number of patients with mild to moderate SNHL had positive *GJB2* screens.**

CONCLUSIONS: **Based on diagnostic yields, we propose a cost-effective stepwise diagnostic paradigm to replace the more commonly used and costly simultaneous testing approach. EBM rating: C.** (Otolaryngol Head Neck Surg 2004;131: 804-9.)

Moderate to profound congenital sensorineural hearing loss (SNHL) in the United States is estimated to occur in 1 to 2 per 1000 births.[1] Its etiology has historically been classified as either hereditary or acquired. Improvements in prenatal, neonatal, and pediatric care have, however, led to a decrease in the incidence of acquired etiologies, and it is now estimated that up to 50% of all cases are genetic in origin.[2] Most (80%) of these cases are transmitted in an autosomal recessive manner.[3]

Determination of the specific etiology of childhood SNHL is sometimes made from case history review or physical examination. In 22% to 35% of cases, the review may reveal environmental causes such as intrauterine infections, ototoxic medications, maternal or neonatal metabolic disorders, maternal illicit drug use, prematurity, low apgar scores, or exposure to teratogens.[4] Physical examination may show dysmorphisms and syndromes that may be associated with SNHL. More frequently, the etiology of SNHL cannot be diagnosed on history and physical examination alone, and remains unknown. To assist in the diagnosis of patients with idiopathic SNHL, clinicians often enlist the collaboration of other specialists, and typically order an extensive battery of laboratory tests, including complete blood count (CBC), thyroid function tests, erythrocyte sedimentation rate (ESR), urinalysis, syphilitic antibody blood titers, cholesterol and triglyceride blood levels, blood chemistries, and an electrocardiogram (ECG). Though the SNHL-specific diagnostic yield of these tests has been reported to be as low as 0% to 2%,[4,5] this simultaneous diagnostic approach to laboratory testing continues to be used.

High-resolution radiographic imaging studies and genetic testing are now added to this protocol and performed concurrently. An invaluable diagnostic tool, temporal bone imaging has revealed abnormalities in up to 39% of children with SNHL.[4] Of relevance in genetic testing, in 1997, the gap junction beta 2 gene

Preciado et al.
Otolaryngology-HNS
2004; 131: 804-9

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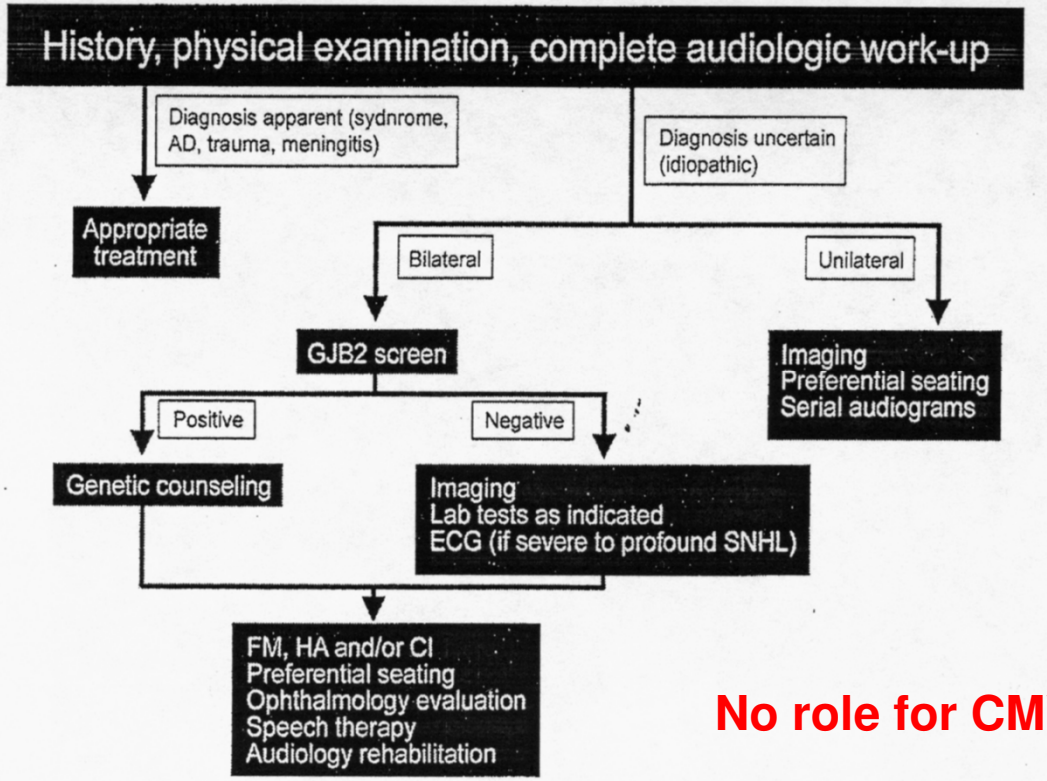
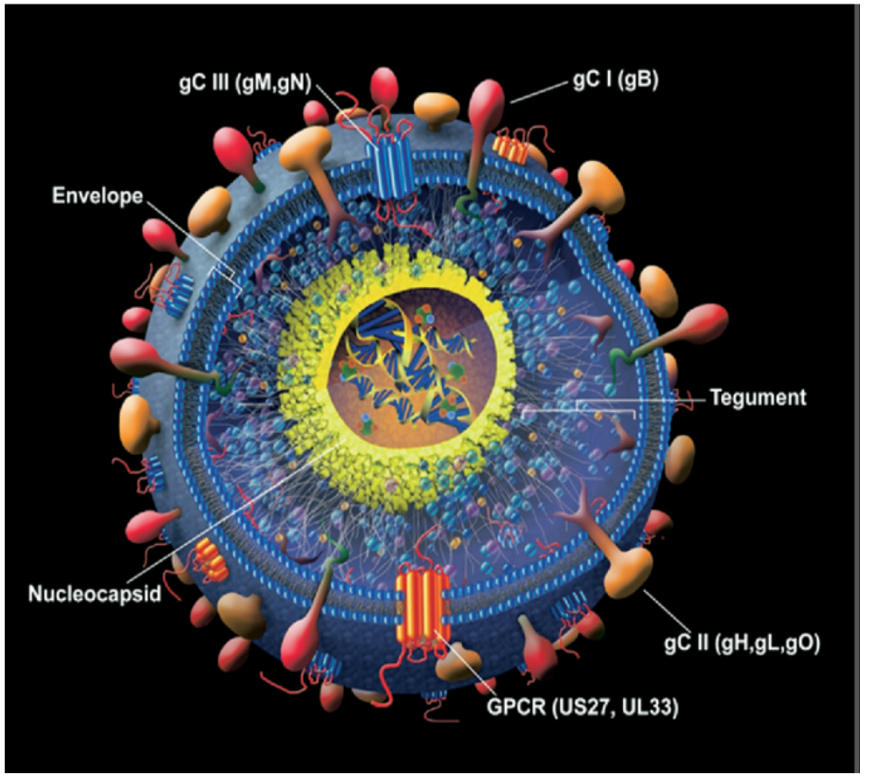


No role for CMV testing?

What is Cytomegalovirus?

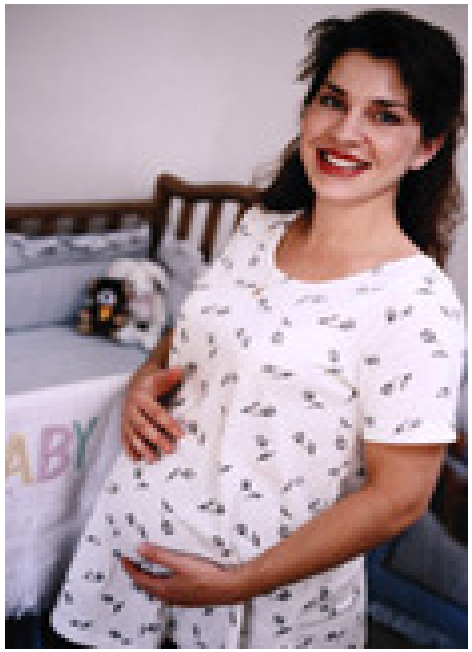
- A Herpesvirus
- Species specific (only infects humans)
- CMV most common cause of nonhereditary SNHL
- May account up to **33%** pediatric SNHL[1]
- Cost C-CMV greater than $ 4 billion/yr in US



[1]Hicks T, et al. Congenital Cytomegalovirus infection and neonatal auditory screening. J. Pediatr 123: 779-82, 1993

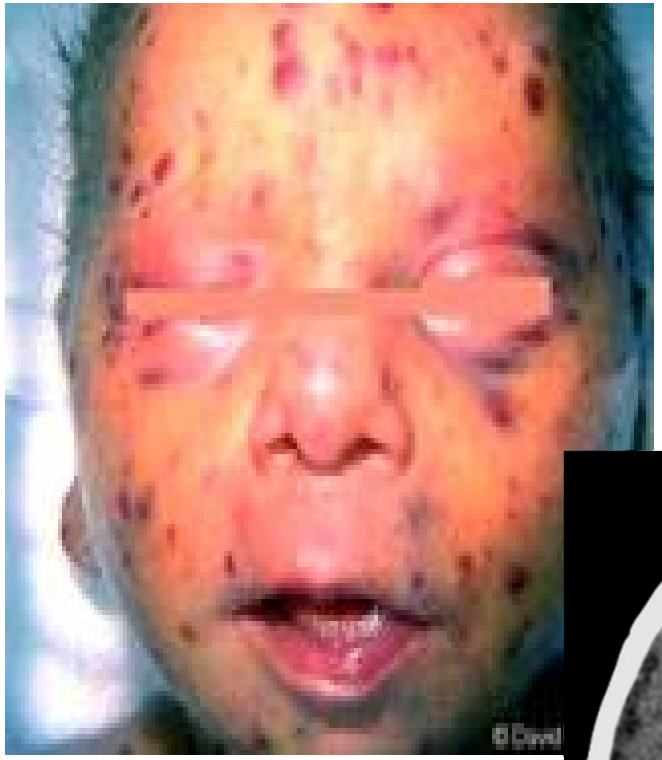
Transmission Mother to Fetus:

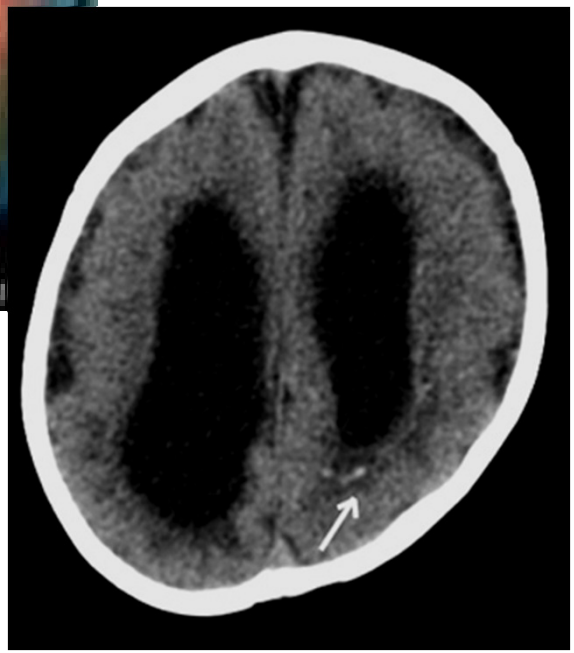
- Seronegative moms
- Seropositive moms
- Infant presentation
  - Symptomatic (evident at birth) — 5%-10%
  - Asymptomatic (silent at birth) — 90%-95%



CMV: Symptomatic Congenital Infection

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



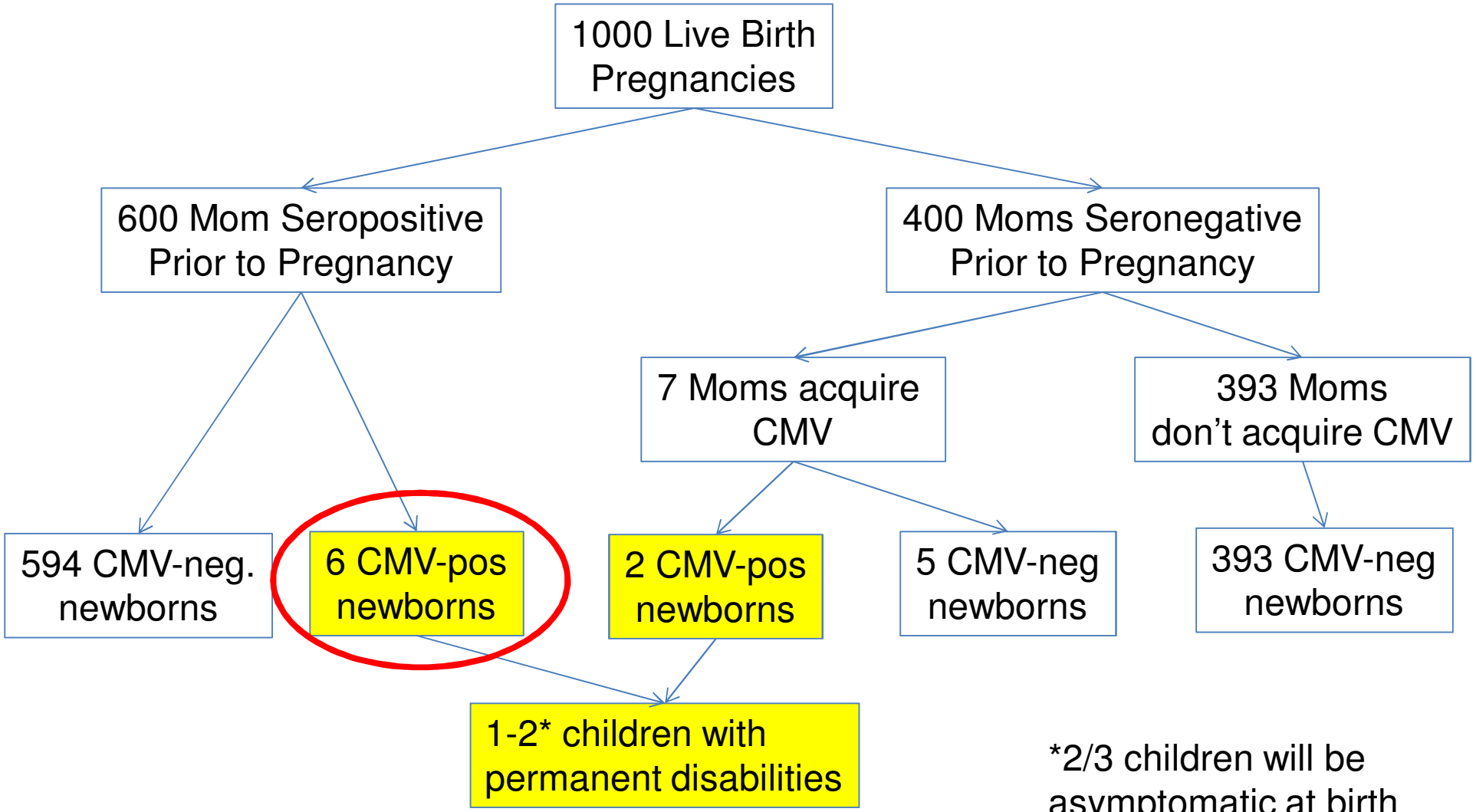


CMV: Asymptomatic Congenital Infection

- >90%
- 5- 15% have sensorineural hearing loss that can be evident at birth or appear **later** in childhood

Disease Burden of CMV in the US:

From: Cannon, Grosse and Fowler. Epidemiology and Public Health Impact…CMV, 2013



*2/3 children will be asymptomatic at birth

Why Seropositivity can result in Congenital Infection?

Infection with Different CMV strain between pregnancies	Mothers of Infected Infants (n= 16)	Mothers of Uninfected Infants (n=30)	P-Value
Yes	10 (62%)	3 (13%)	P < 0.001
No	6 (38%)	26 (87%)	

Acquisition of new CMV strains increases number of mothers with infected infants

NEJM 2001; 344: 1366-1371

Challenge of Vaccination:

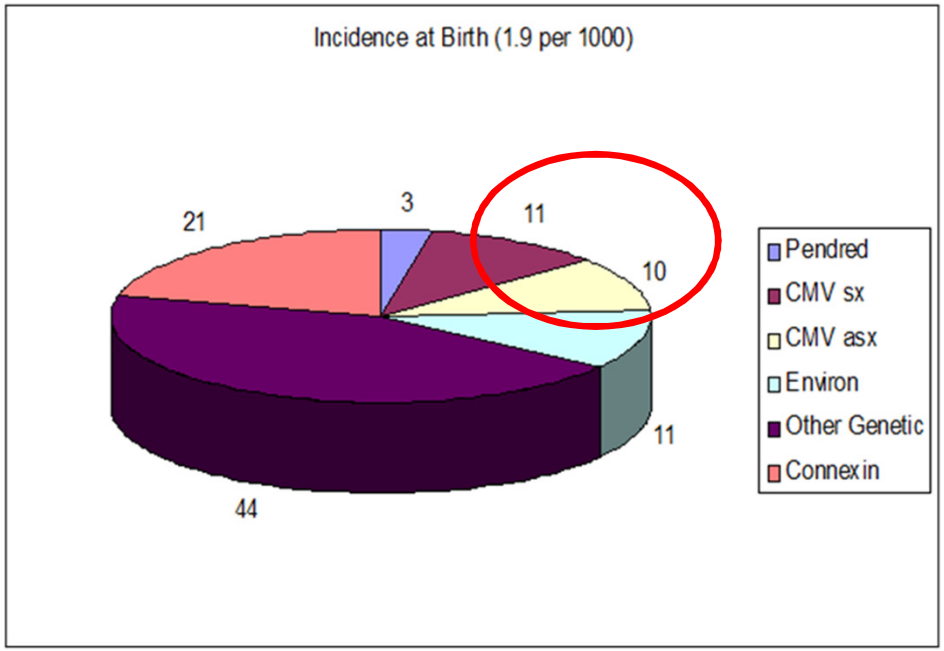
- No commercially licensed vaccine available for CMV

“The Challenge with vaccination for congenital CMV is the need for a vaccine to be better than nature.”

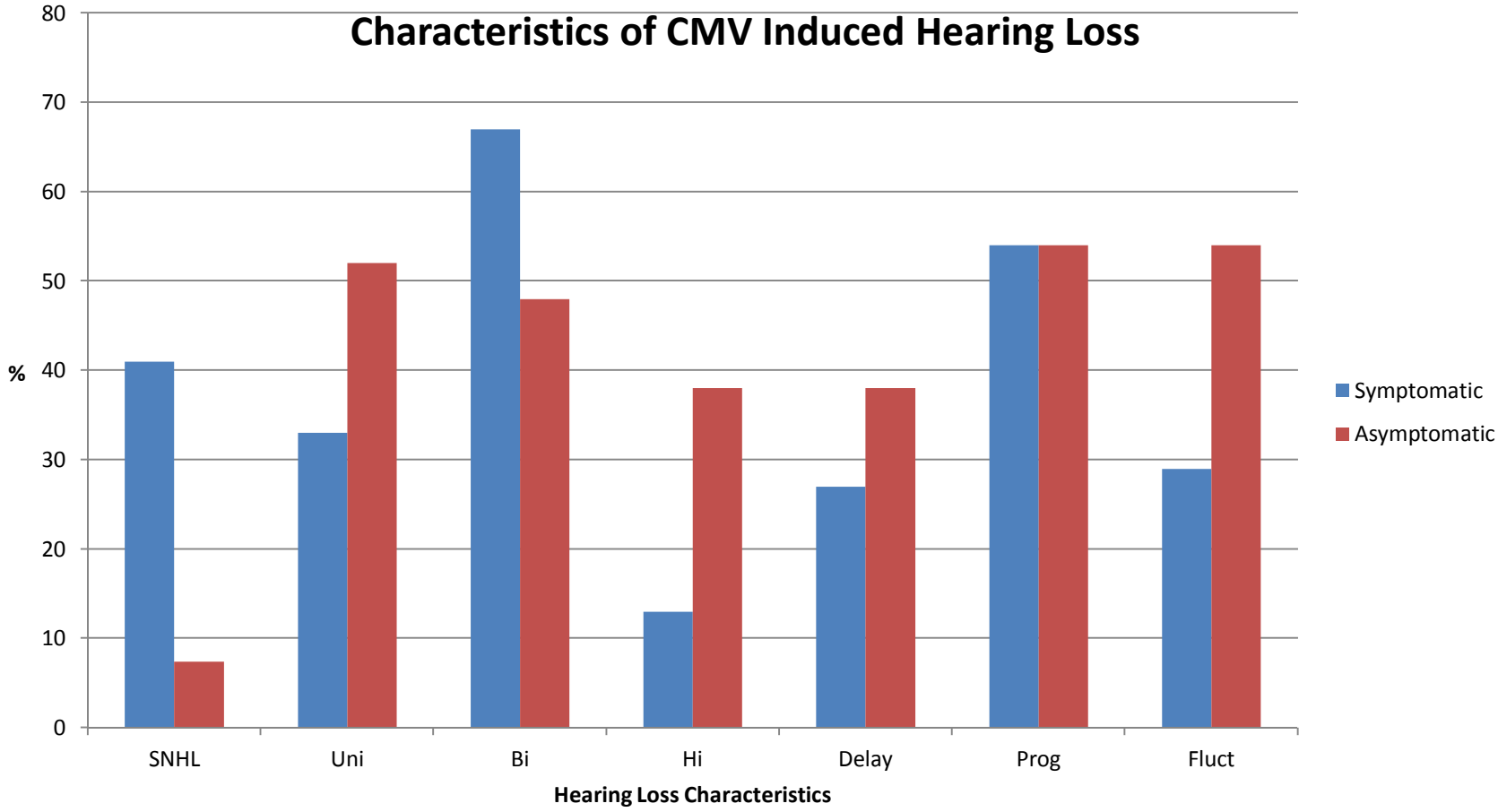
David Kimberlin

Audiologic Sequelae from Congenital CMV:

- Grosse et al. 2008
- Morton et al. 2006

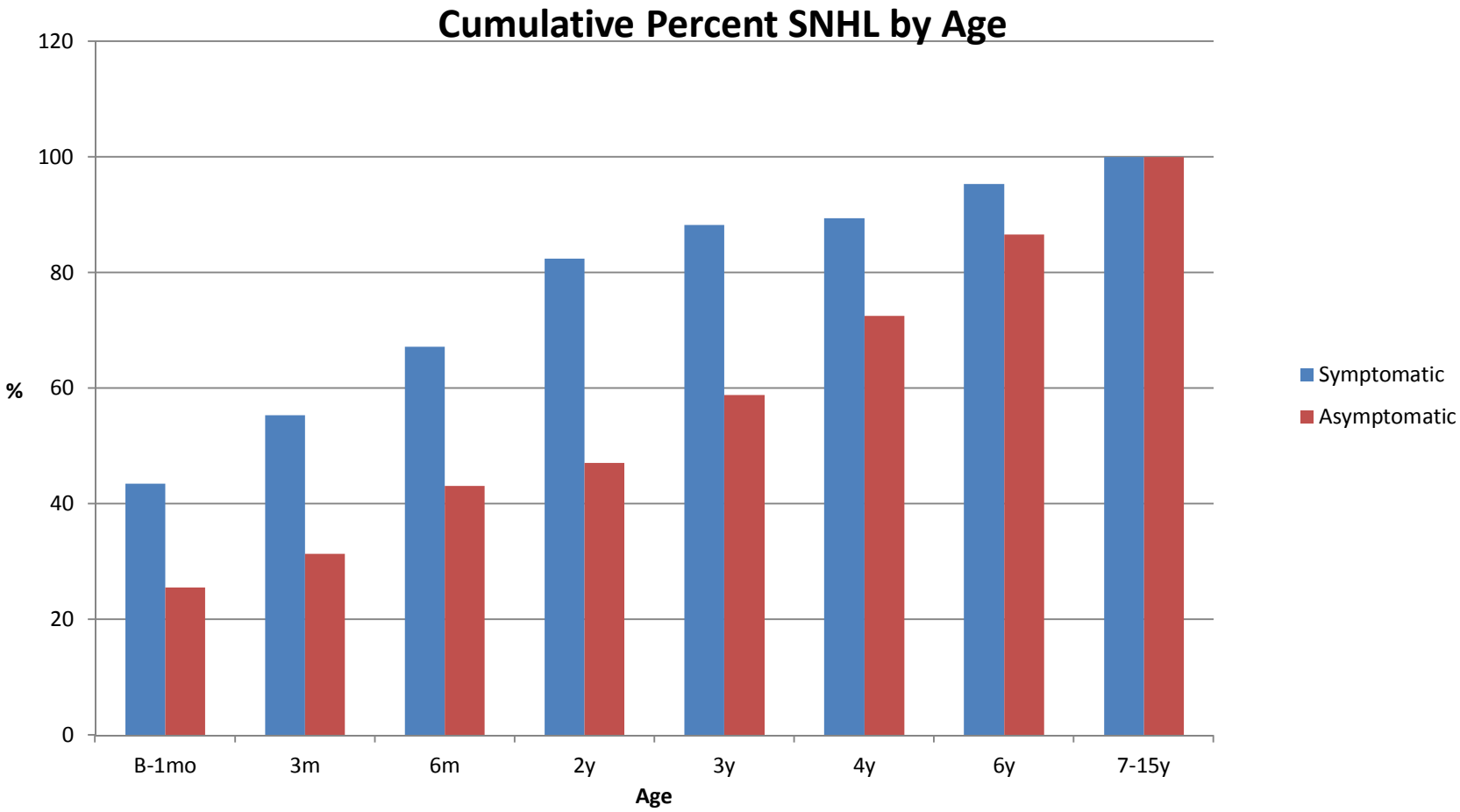


Audiologic Sequelae from Congenital CMV:



Dahl et al. J Am Acad Audiol 2000; 11: 283-290

Nature of Progressive SNHL:



Dahl et al. J Am Acad Audiol 2000; 11: 283-290

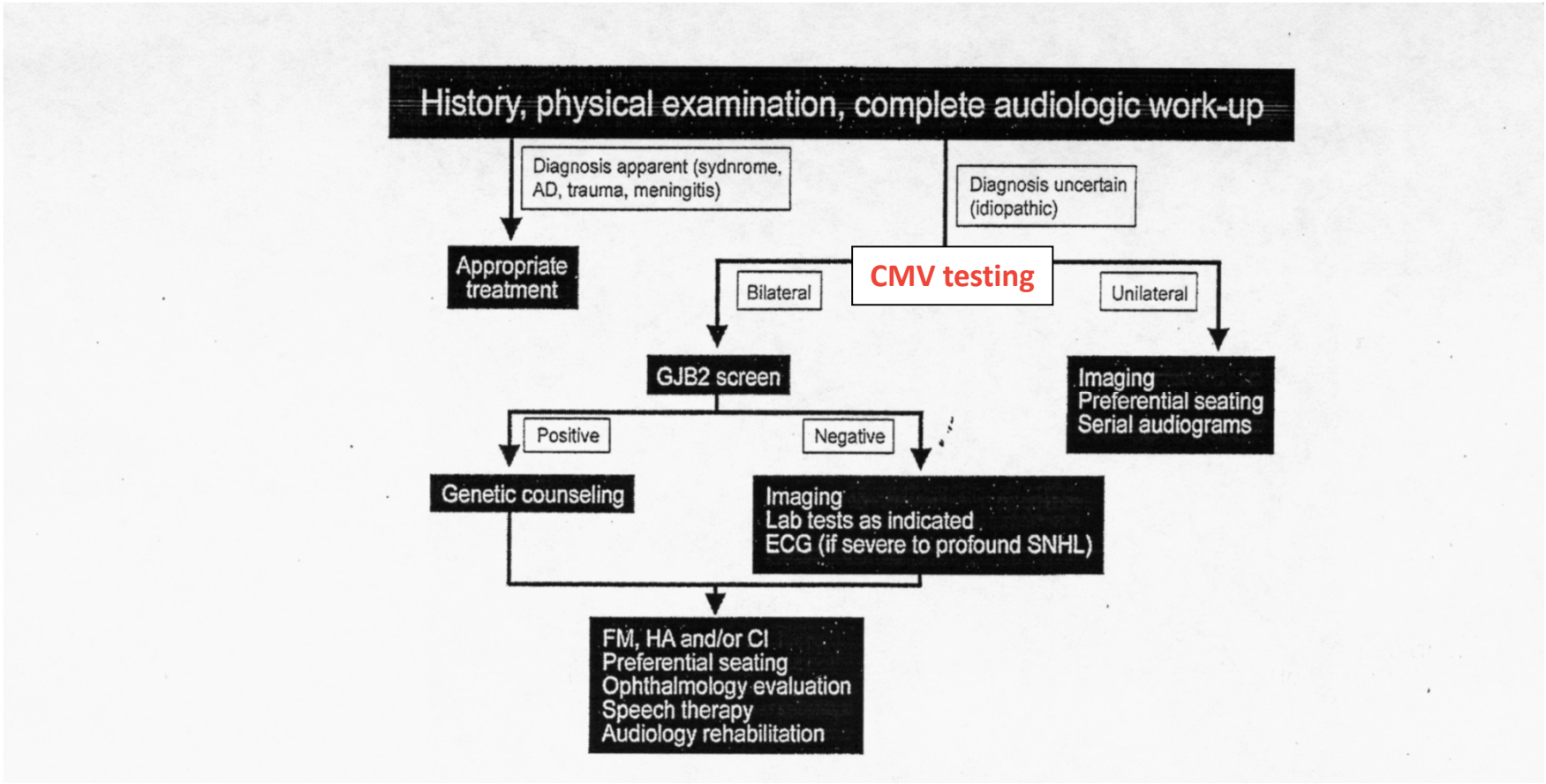
Nature of CMV Induced SNHL (Summary):

- CMV makes up to 21% cases of pediatric SNHL
- Can present at birth but frequently presents later in life
- Type and severity of hearing loss variable
- Progression and fluctuation of HL common

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss – Utah Experience

- What happens if you look for CMV?
- May 2008 started to incorporate CMV testing
- Sequential diagnostic paradigm

"New Current" Approach to Pediatric SNHL



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

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- **Confirmed Diagnosis-** positive urine or saliva CMV PCR infant < 3 weeks OR positive result infant > 3 weeks AND positive DBS

- **Probable Diagnosis-** - positive urine or saliva > 3 weeks of age AND CNS findings or progressive SNHL

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- 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

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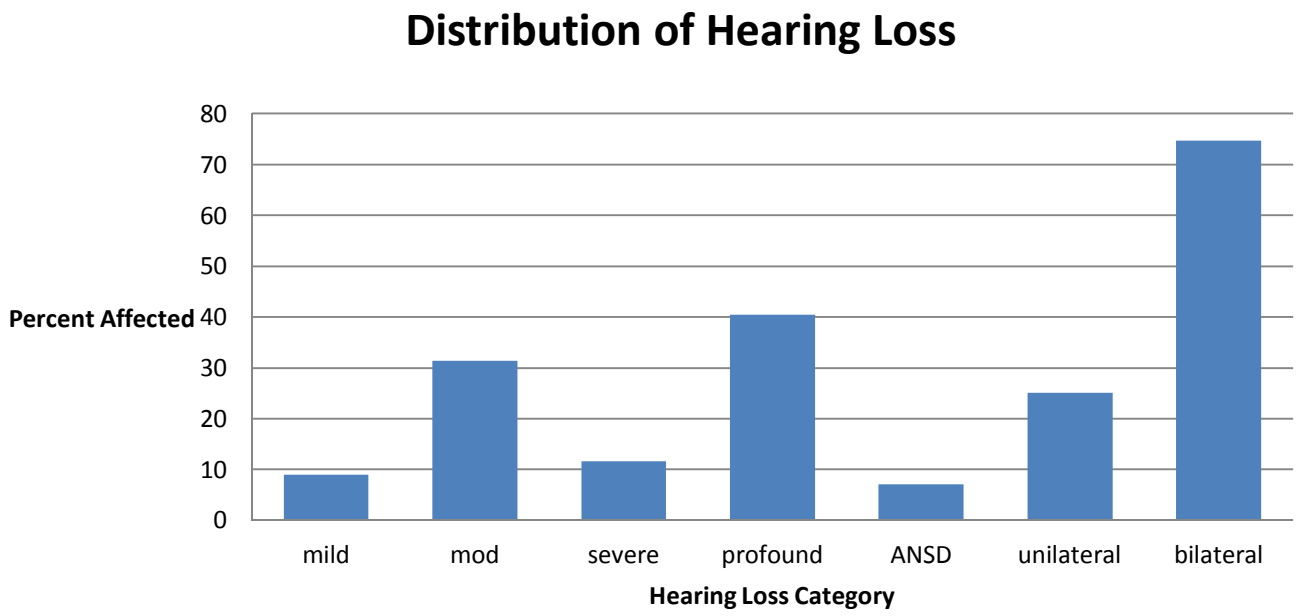
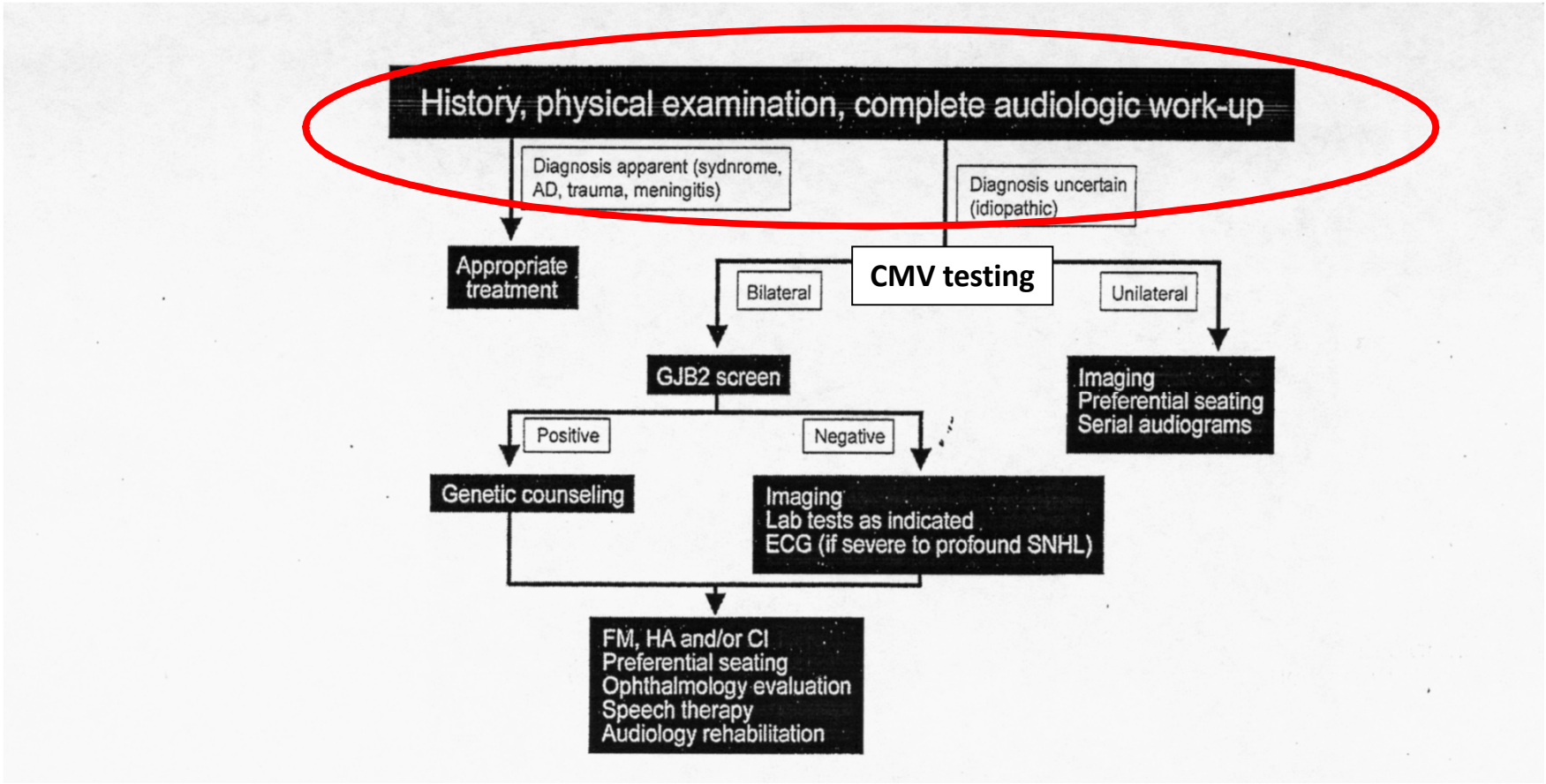
- RESULTS:
- N=111 children w SNHL (2008-2013)



"New Current" Approach to Pediatric SNHL



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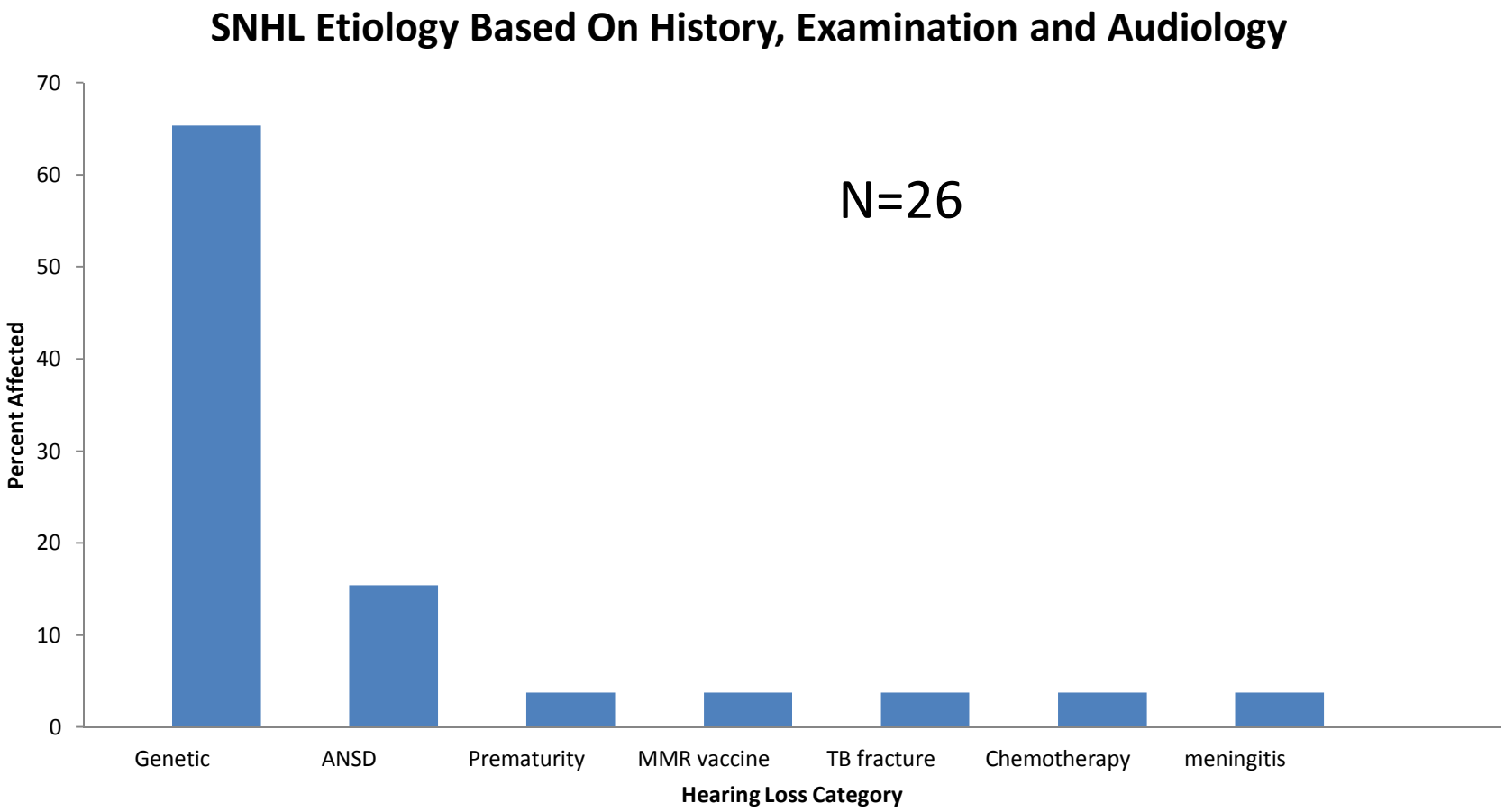
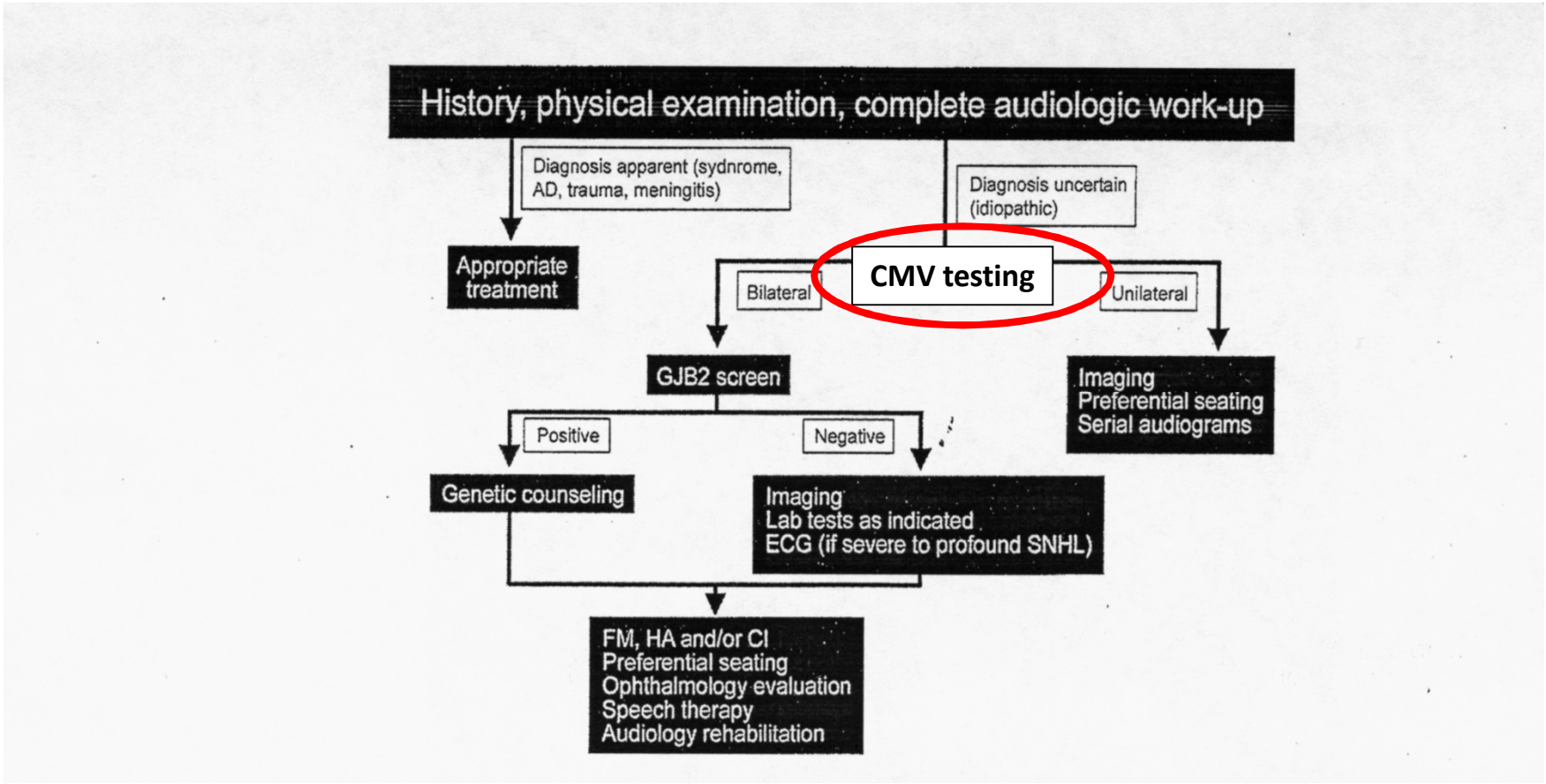


"New Current" Approach to Pediatric SNHL



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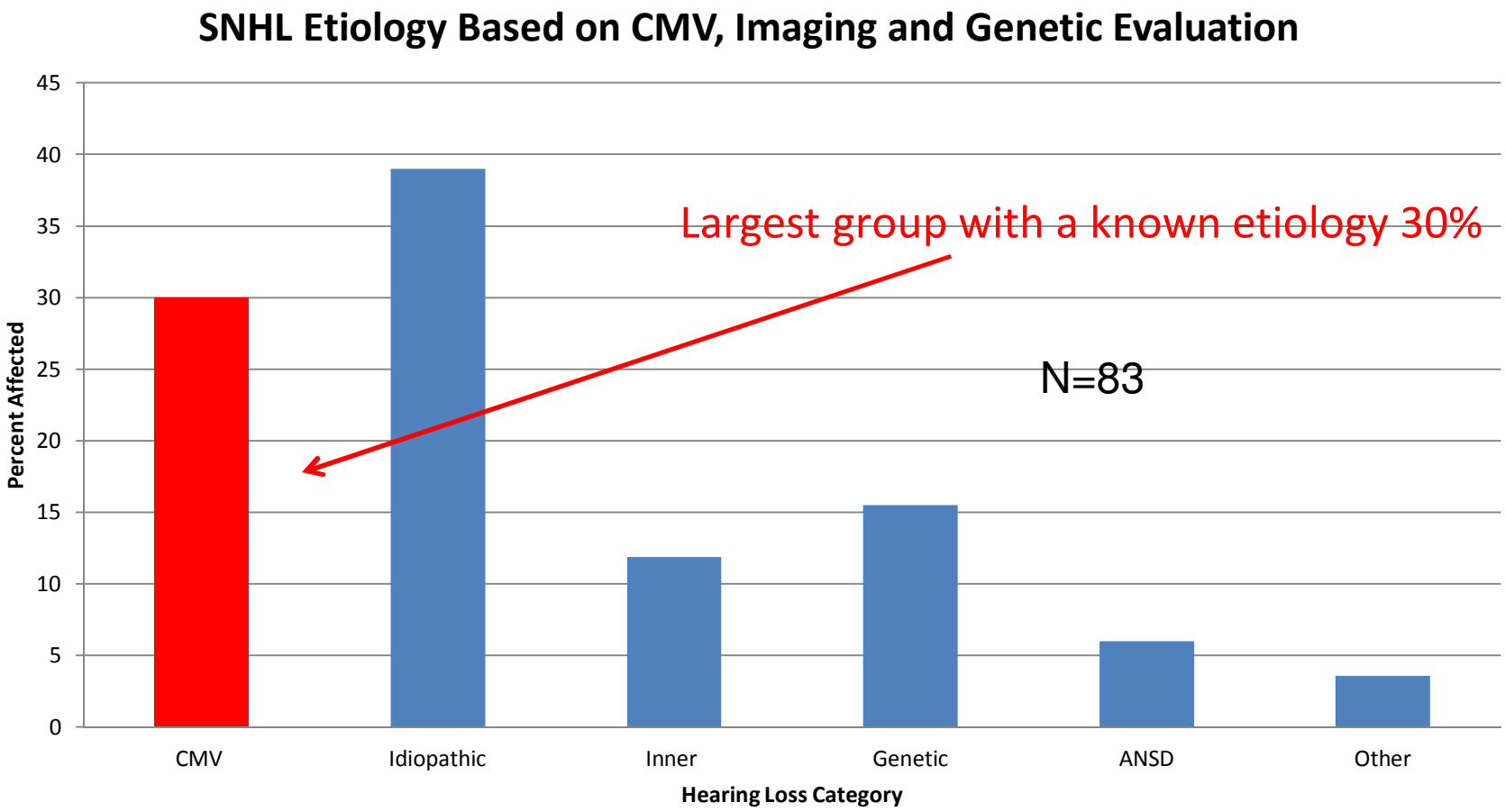


The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

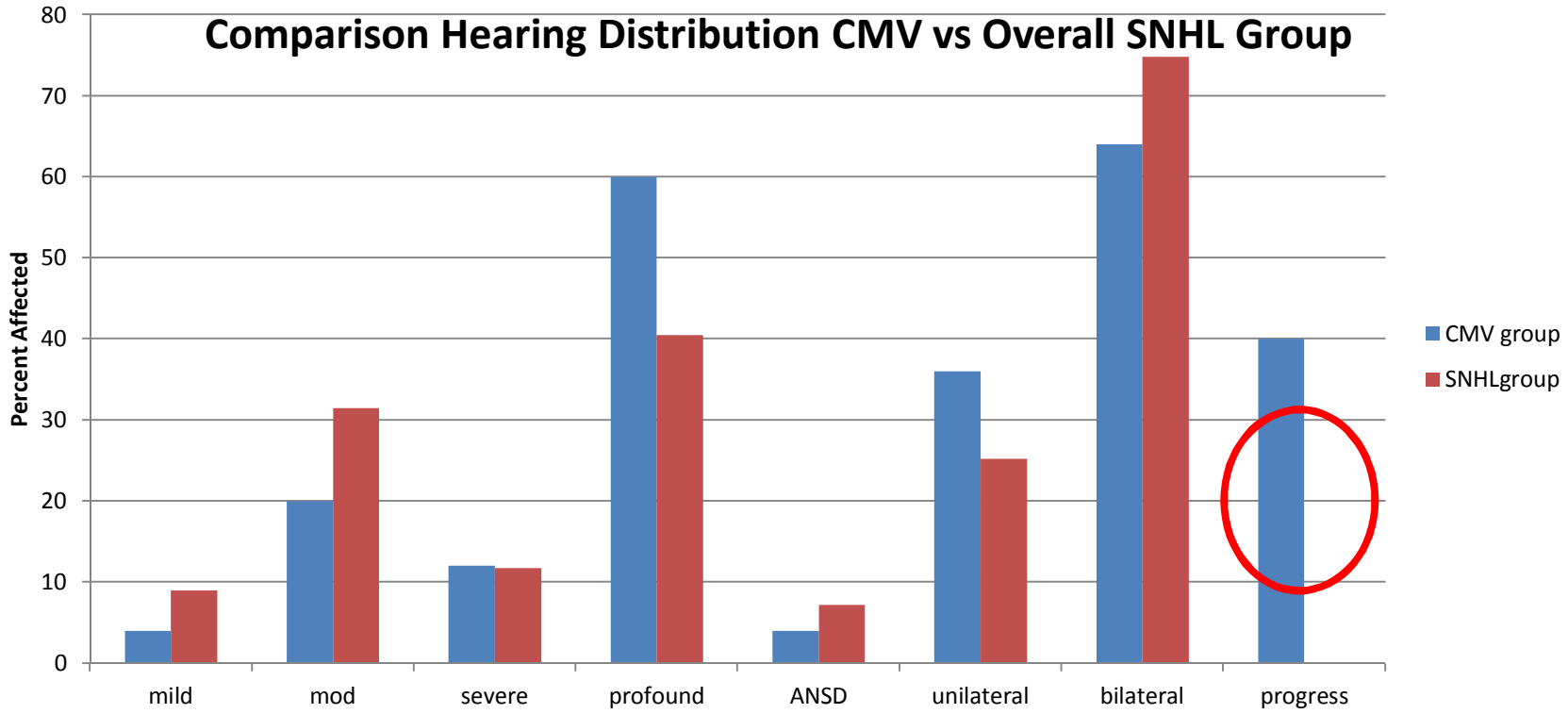
- Breakdown of CMV Patients (n=25)
- Sixteen – confirmed CMV diagnosis
- Six of sixteen diagnosed via DBS testing
- Nine- probable CMV diagnosis

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

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

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Distribution of CMV vs SNHL Groups:



Cost Estimates of Alternative SNHL Evaluation Approaches Based on Diagnostic Yield (Based on Testing 100 children with SNHL)

Testing	Bilateral Mild	Bilateral Mod-Severe	Bilateral Severe-Prof	Unilateral	ANSD	Overall
GJB2 screen[1]	15%	5%	37.7%	0%	0%	19%
Imaging	0%	8%	0%	18%	50%	11%
CMV PCR	20%	23%	36%	36%	17%	30%
Simultaneous	$226,907	$226,907	$226,907	$226,907	$226,907	$226,907
GJB2 screen	$66811	$218,619	$163,920	N/A	N/A	$195,413
Imaging	N/A	$221,482	N/A	$164,490	**$162,426**	$214,023
CMV PCR	**$55,579**	**$176,249**	**$147,617**	**$147,617**	$189,464	**$160,832**

[1]Diagnostic yield based on Preciado et al. and Dent et al. study

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

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Is CMV diagnosis for SNHL patients helpful?
- Are we jumping the gun?

CMV diagnosis

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

“Prevention is better than cure.”

Desiderius Erasmus

Prevention of CMV:

- Child with congenital CMV will shred virus for months or years- “contagious”
- Good hygiene

Prevention of CMV:

- 14 seronegative pregnant women -behavioral intervention resulted in no seroconversion
- 5000 seronegative pregnant women – behavioral intervention > 50% drop expected rate seroconversion

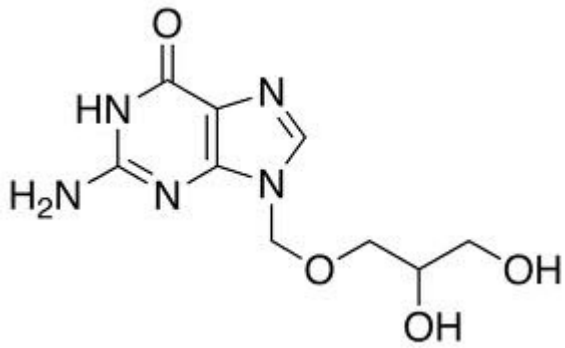
Alder et al, 1996; Picone et al. 2009; Vauloup-Fellous et al, 2009

Other Benefits from Early CMV Diagnosis:

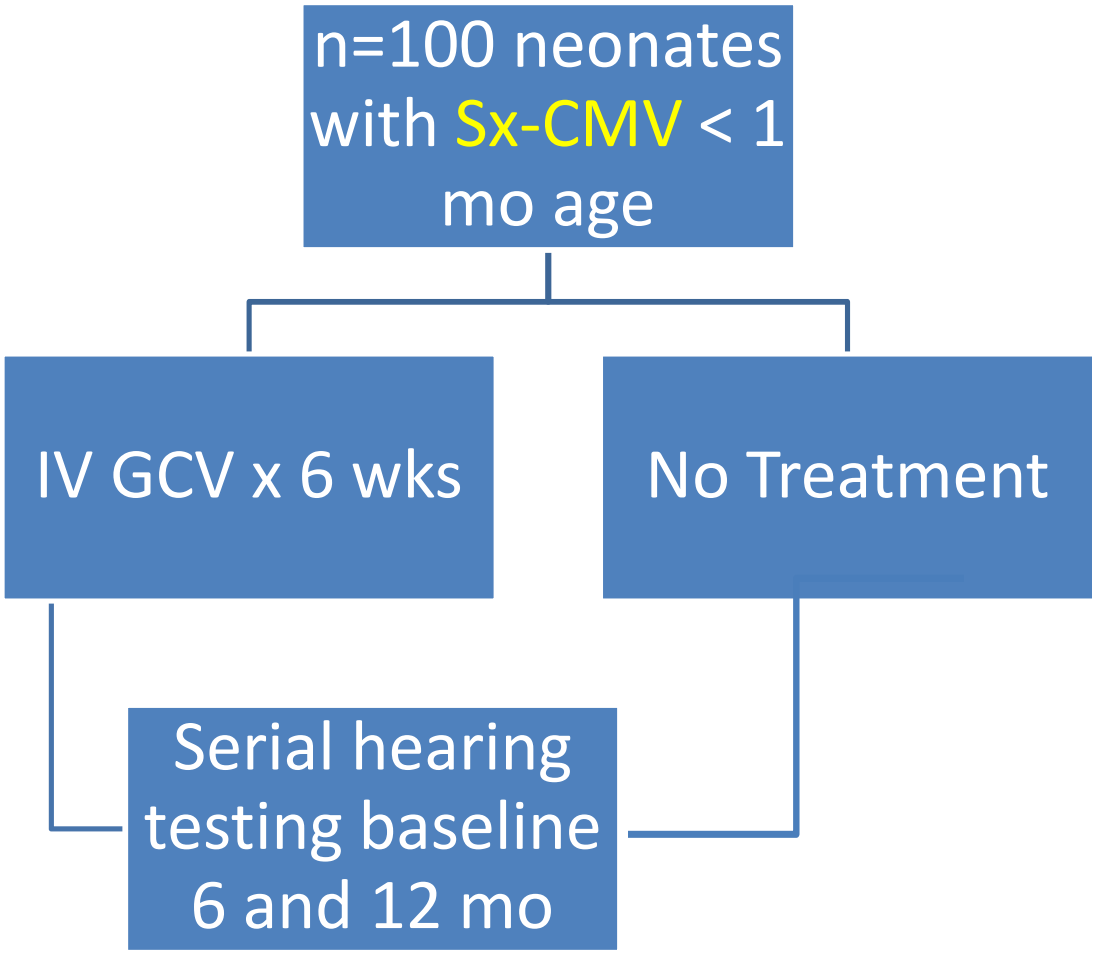
- Identify at risk group -audiologic testing
- Obviates need other unnecessary testing
- May direct to other testing
- May impact on treatment (e.g. antiviral therapy)

Ganciclovir:

- 1st antiviral agent approved for CMV treatment (1994)
- synthetic analogue of 2’-deoxy-guanosine
- Inhibits viral DNA polymerase
- Requires parenteral administration

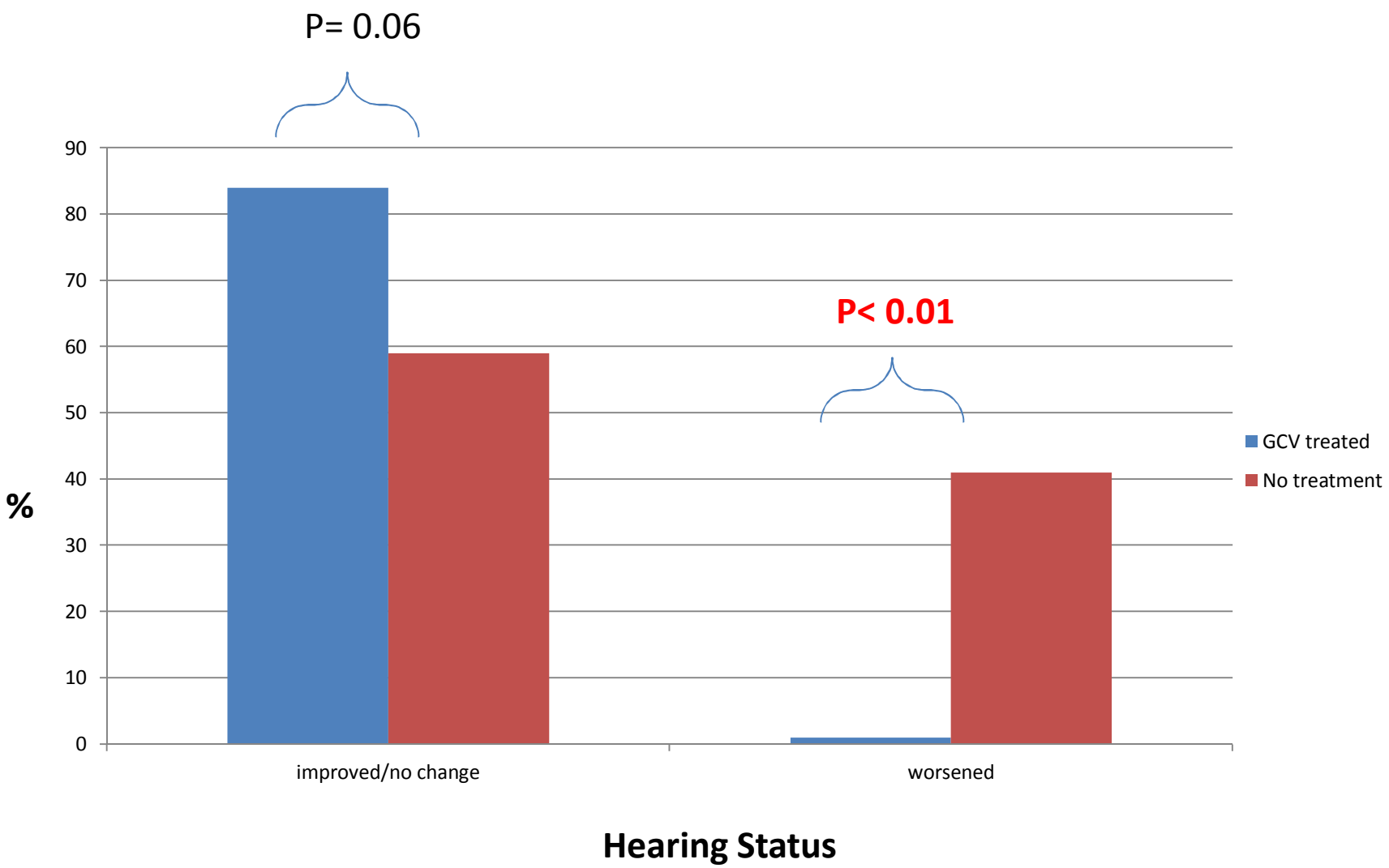


Role for Antiviral Therapy?

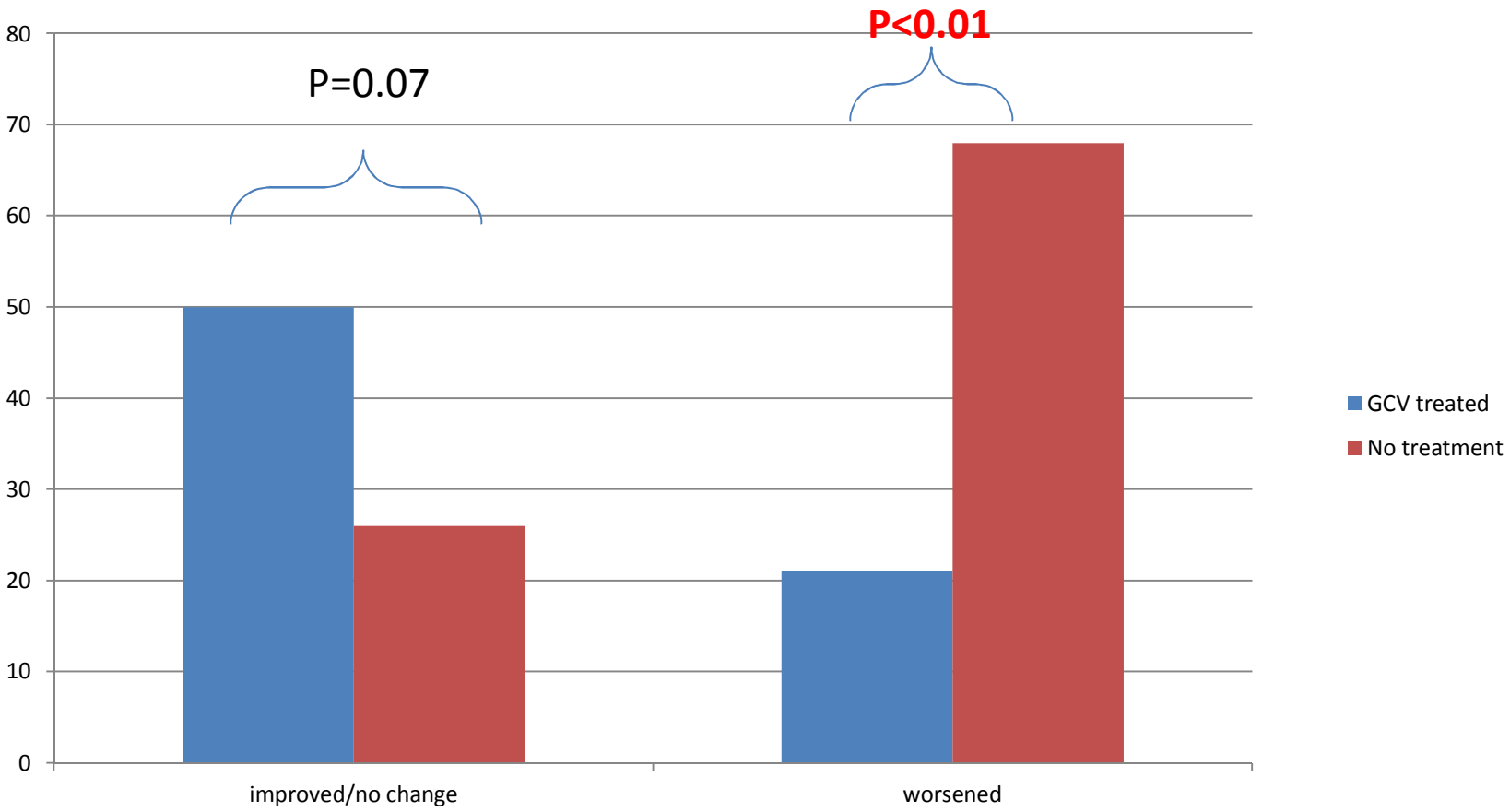


Kimberlin D. et al. Effect of Ganciclovir on Hearing …Pediatrics 143: 16-25., 2003

Hearing Outcomes at 6 mo



Hearing Outcomes at 12 mo



Adverse Effects From GCV:

- 29 of 46 GCV rx'ed (63%) had grade 3 or 4 neutropenia during rx vs 9 of 43 (21%) controls $p < 0.01$
- Mean time onset neutropenia: 14 days for both
- 3 GCV recipients had catheter infections
- 1 GCV recipient transient Gm (-) septicemia

Conclusions from Study:

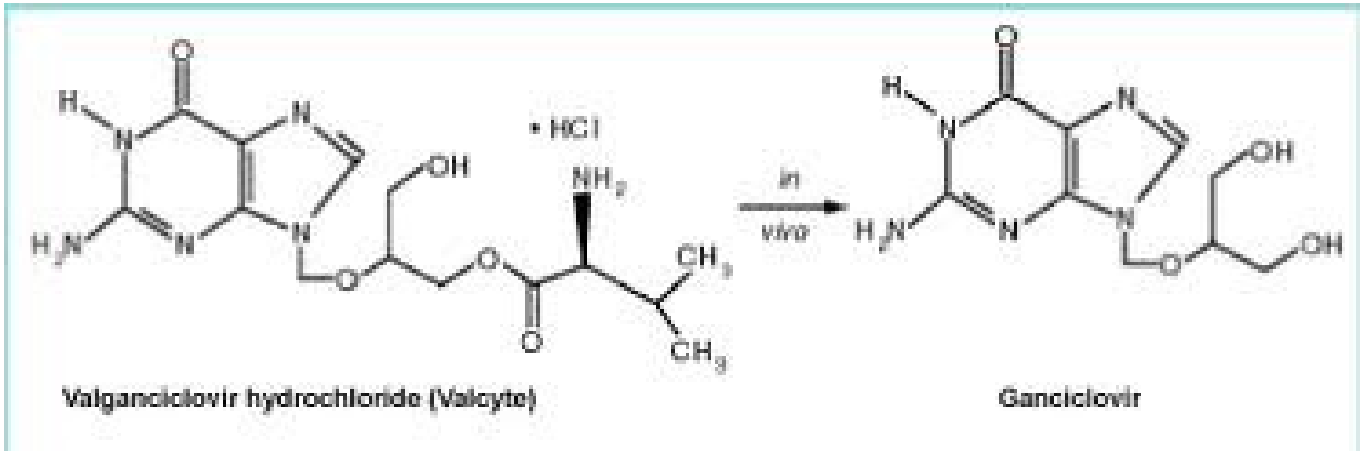
- GCV therapy begun within 1st mo life in symptomatically infected infants prevents hearing deterioration at 6 mo and may prevent at > 1 year
- Almost 2/3 treated infants have significant neutropenia during therapy.

Limitations of the Study:

- Of the 100 enrolled patients from 18 CASG sites, only 42 met all the study entry criteria
- Large number of patients not evaluated for the primary end point may affect results
- Applies to children with "**symptomatic** CMV"
- Relevance to "real" world- e.g. having families stay in house for 6 wk IV therapy
- Concerns with GCV- neutropenia, gonadal toxicity and carcinogenicity in animal models

Valganciclovir:

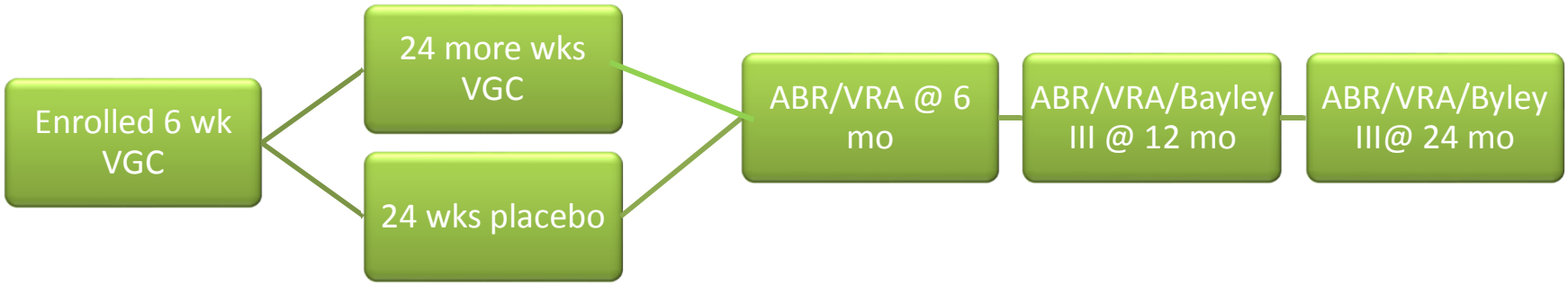
- L-valyl ester prodrug of ganciclovir
- After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases



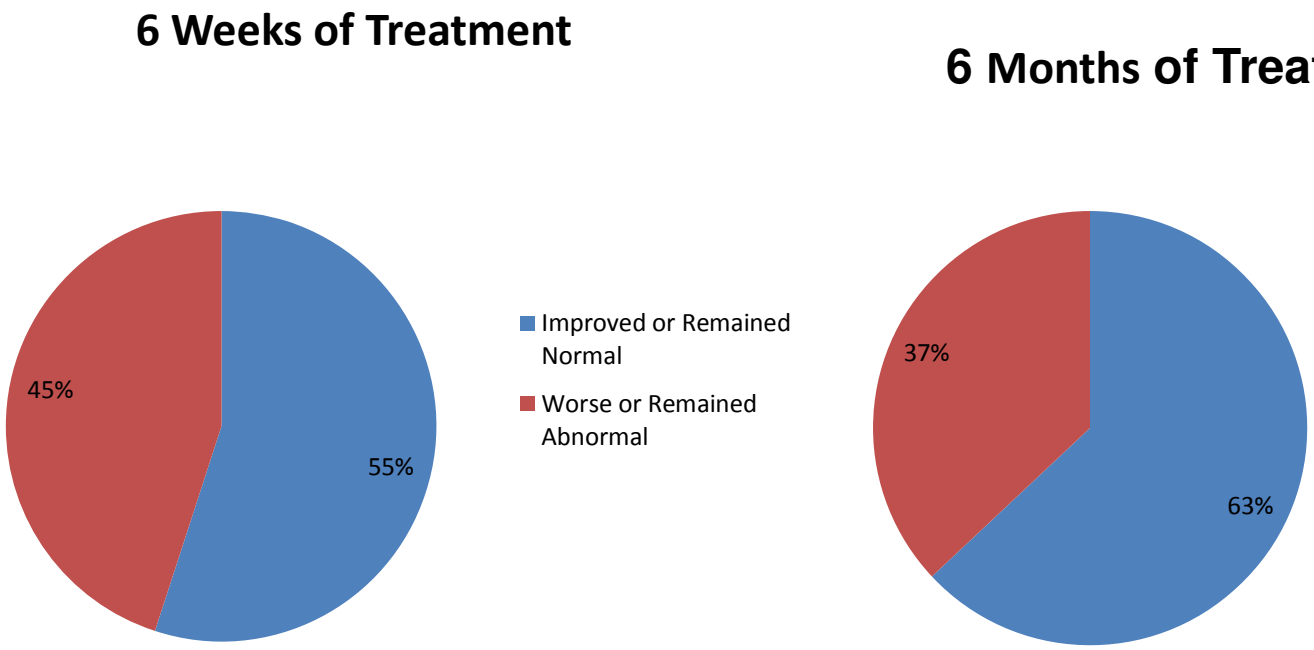
Six Months versus 6 weeks Valganciclovir (VGC) for infants with Symptomatic CMV

- Confirmation CMV from urine or throat swab-culture, shell vial or PCR
- Symptomatic CMV (1 or more): thrombocytopenia, petechiae, HSM, IUGR, hepatitis, CNS involvement (hearing loss, radiographic, CMV in CSF)
- <30 days
- Weight > 1800 grams
- Gestational age > 32 weeks

Six Months versus 6 weeks Valganciclovir (VGC) for infants with Symptomatic CMV



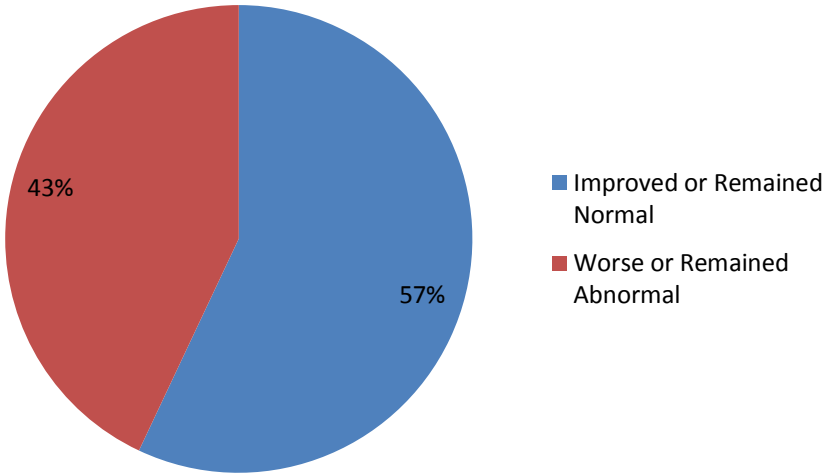
6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ 6 mo



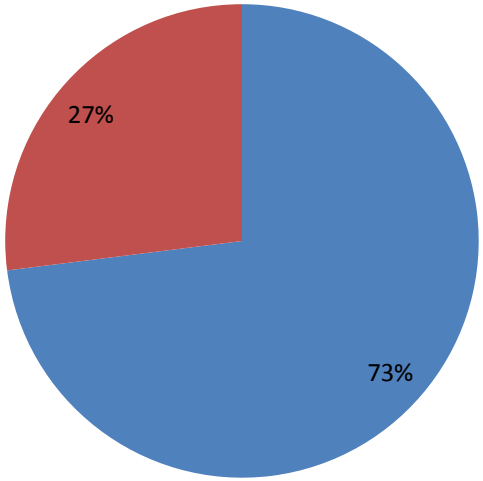
P=0.19

6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ 12 mo

6 Weeks of Treatment



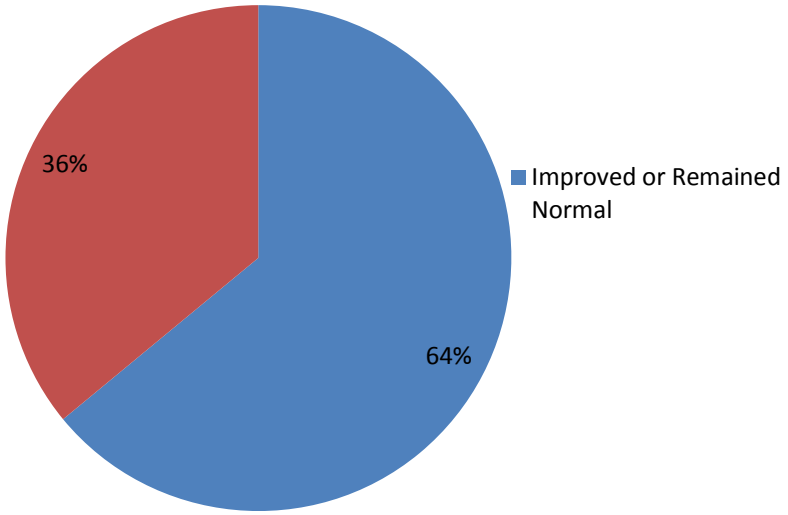
6 Months of Treatment



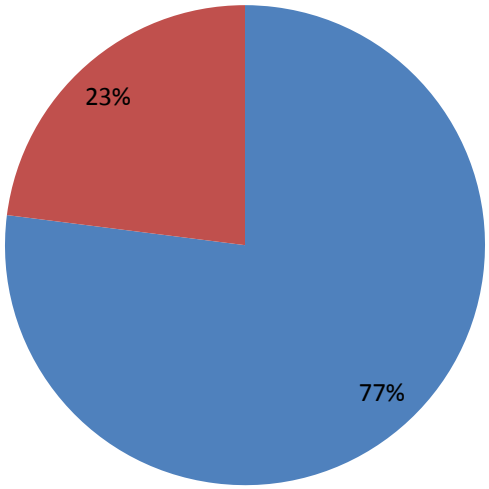
P= 0.01

6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ 24 mo

6 Weeks of Treatment



6 Months of Treatment



P= 0.04

Bayley III Developmental Scale Qualitative Descriptors of Composite Scores

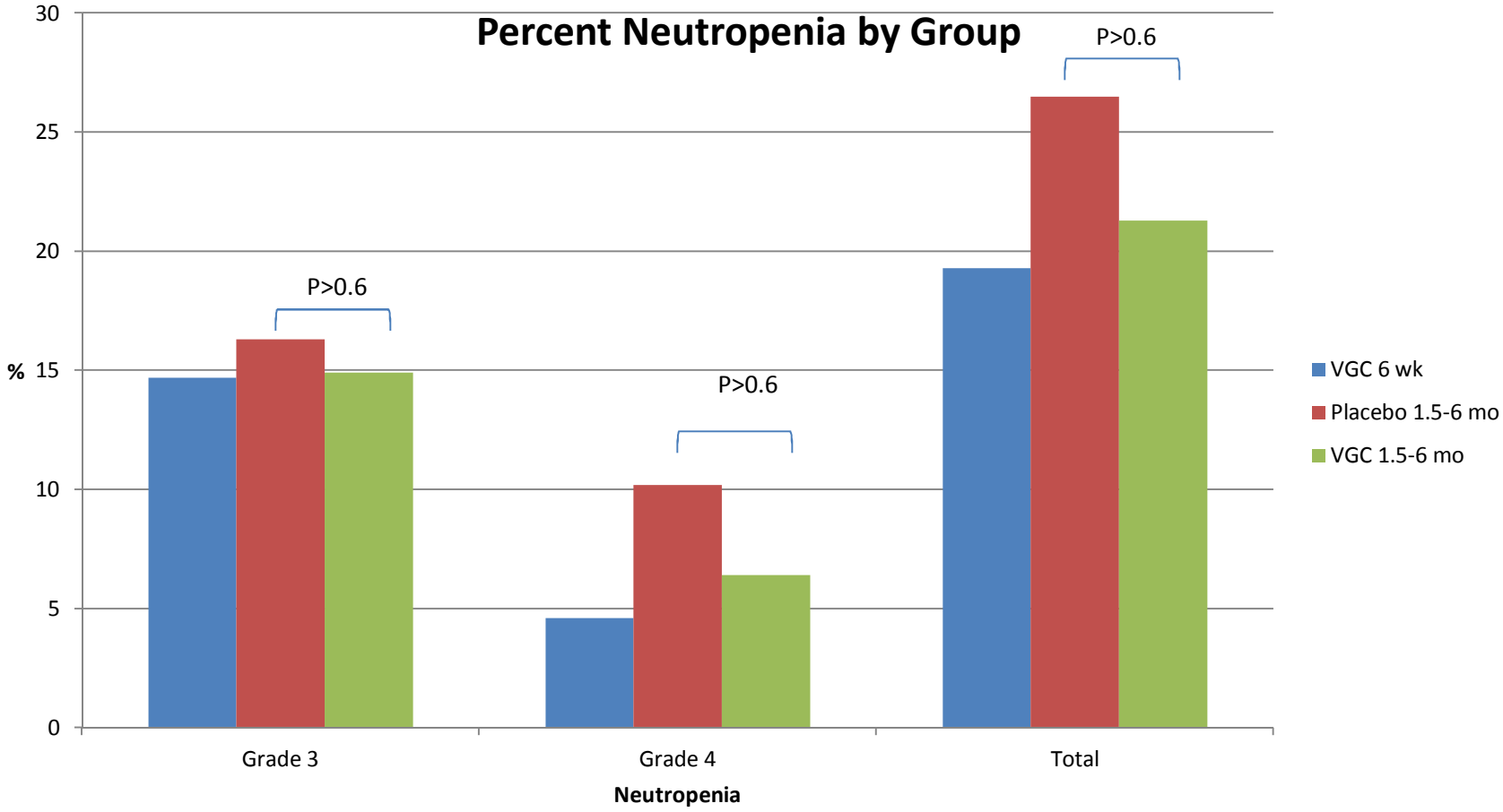
Composite	Classification
130 and above	Very superior
120-129	Superior
110-119	High average
90-109	Average
80-89	Low Average
70-79	Borderline
69 and below	Extremely low

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

Neutropenia by Group:



Neutropenia from VGC Trial

- Three subjects had VGC dose temporarily held for ANC < 500 (All first 6 wk treatment)
- No excess neutropenia with continuation of VGC treatment from 6 weeks to 6 mo compared to placebo

Conclusion from 6 wk vs 6 mo VGC Trial:

- 6 mo VGC rx infants w sx congenital CMV improves audiologic and neurodevelopmental outcomes to at least 2 years of age
- Less neutropenia seen during first 6 weeks than seen in an earlier CASG study of IV GCV
- No excess neutropenia w continuation of VGC from 6 weeks to 6 mo. compared to placebo

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

"Medical science has proven time and again that when the resources are provided, great progress in the treatment, cure, and prevention of disease can occur."

Michael J. Fox

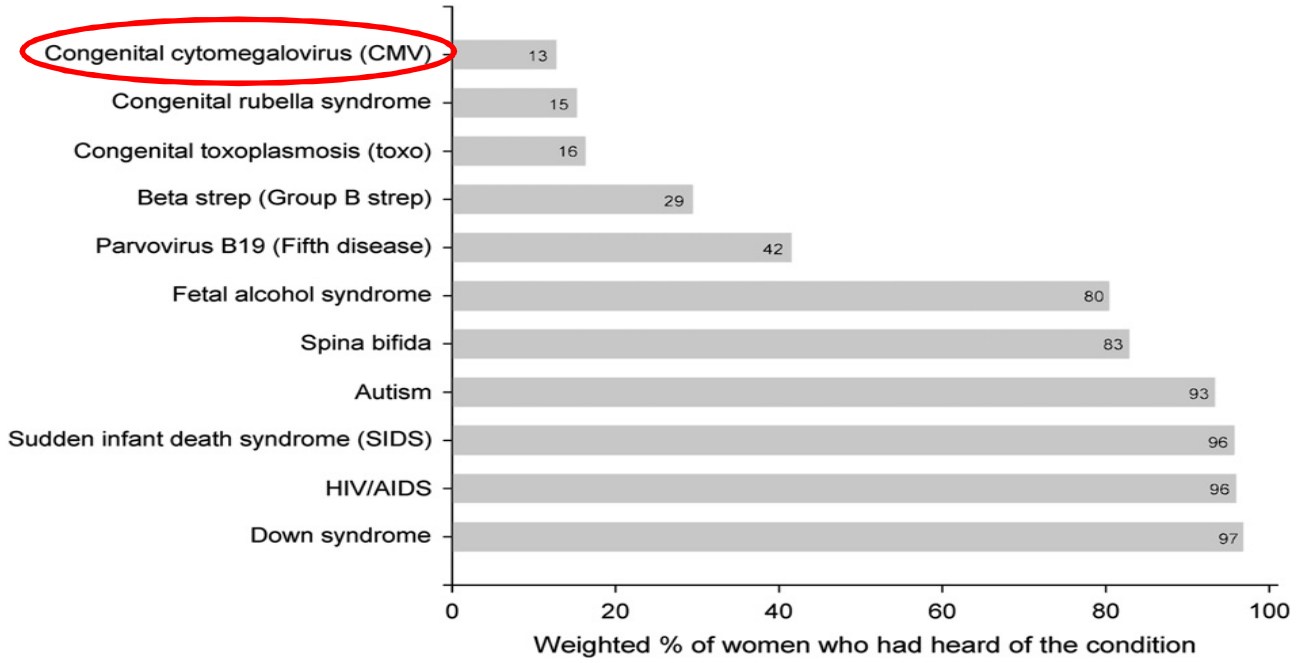
Utah CMV Law:

- Passed July 2013
- Charges Utah Dept Health oversee

1. Educational programs to increase awareness of this condition
2. CMV testing newborns who fail 2nd hearing screen at 3 weeks of age or younger

Awareness of CMV:

- Survey 4184 participants (HealthStyles survey)
- 7% men and 13% women had heard of CMV
- High incidence of high risk behaviors for transmission



Incorporation NBHS for CMV testing (Advantage):

- Uses an existing screening program to diagnosis a common cause of SNHL (NBHS)
- The number of infants undergoing CMV testing is manageable
- The method of testing is easy to perform
- The cost of testing is relatively inexpensive
- Identifies subset of children with congenital CMV who may benefit from antiviral therapy

Incorporation NBHS for CMV testing (Disadvantage):

- Not all children are screened for congenital CMV infection
- Majority of children who will develop CMV induced SNHL are not tested
- Many families unaware their child has CMV
- Lost opportunity for education, prevention and antiviral therapy

Should we be looking at universal CMV screening?

- NO
- No evidence to support antiviral therapy for CMV infected children without hearing loss
- Significant cost to implement (DBS assay not a good option- poor sensitivity)
- Logistical hurdles

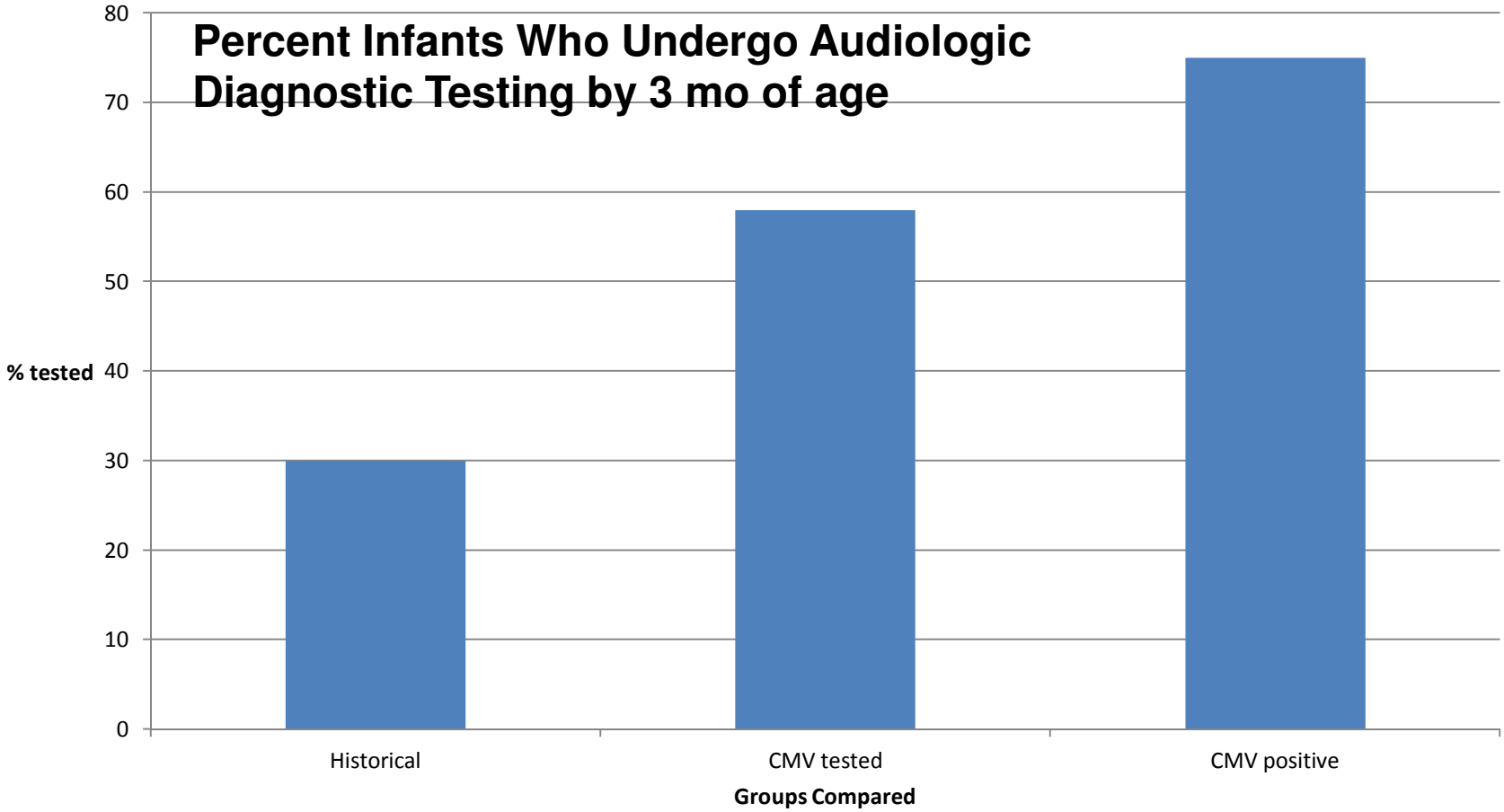
Proposed Approach for Early Detection:

- 3 week old fails NBHS x2 →CMV saliva PCR-positive
- Early intervention services
- Family provided education on CMV
- Audiologic evaluation (ABR) for possible SNHL
- MRI brain/temporal bone
- Antiviral therapy option presented if confirmed SNHL

Early Results from CMV legislation:

- Awareness still a challenge
- Some infants have undergone blood PCR CMV testing not saliva or urine
- 2 false positive saliva CMV results
- Know of 10 infants diagnosed with congenital CMV from Utah law

Early Results from CMV legislation:



Conclusion:

- Rapidly evolving field
- Critical providers, EDHI personnel and caregivers know about CMV
- Diagnosis not difficult
- May be more cost effective as first test for hearing loss etiology
- Increasing evidence early diagnosis potential to improve patient and at risk population outcomes

Acknowledgements: