Considerations for Newborn Screening for Congenital Cytomegalovirus

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Presentation Overview

- Public health newborn screening (NBS)
- NBS criteria applied to cCMV
- Opportunities to build the evidence

Public Health NBS

Why Screen Newborns?

NBS benefits babies by detecting life-threatening diseases **before** symptoms emerge.

- Allows for **early treatment** to improve outcomes
- **May reduce costs** of treating complications

Almost **4 million** infants are screened each year

NBS in the United States

- **Universal** NBS
  - Began in 1960s; now in all states, territories, and jurisdictions
  - **State-sponsored** public health programs
    - **Specific** screening panels—determined by state
- Initial targeted conditions
  - Phenylketonuria and similar conditions
- **Untreated** children suffer enormous challenges
  - Phenylketonuria
    - Relatively normal lifespan
      - **Untreated**: usually intellectual disability with IQ frequently below 20
      - Identified and **treated** from birth: Normal IQ
- **Simple, reliable** screening tests and **proven treatment** efficacy

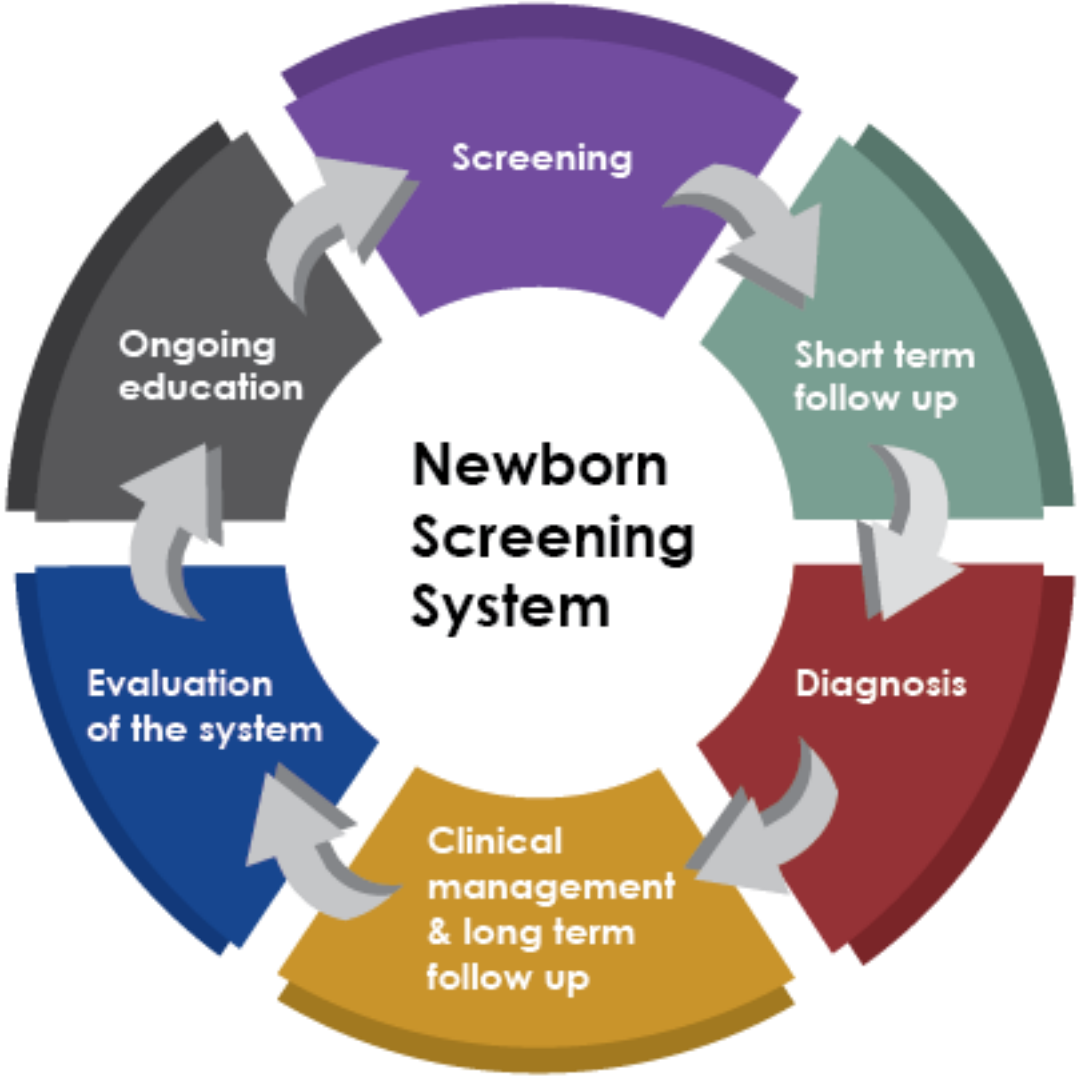
Challenges with NBS in the United States (circa 2000)

- In mid-2000s, **extraordinary variation** from state to state
- Little **systematic evaluation of the rationale** for, and/or the outcomes of, screening

NBS System

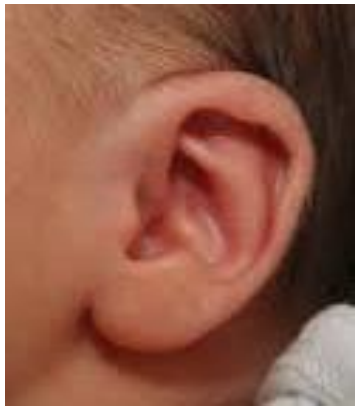
NBS is **more** than a test:

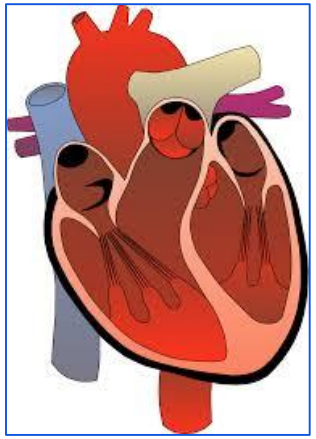
- **Screening**
- Short-term follow-up
- Diagnosis
- **Clinical management and long-term follow-up**
- Evaluation of the NBS system
- Ongoing education—families and healthcare providers



Same Goal for Both Types of NBS

- Two types of NBS paradigms
  - Dried bloodspot (DBS) screening
    - Traditional NBS is a heel prick
    - **Centralized** laboratory testing
  - Point-of-care screening
    - Congenital hearing loss; Critical congenital heart disease (CCHD)
    - **Nursery based screening** with reporting to state health department
- Goal is **timely identification and early intervention** for every baby with an NBS condition





https://www.isns-neoscreening.org/

DBS

- Blood collected via heel prick and spotted on filter paper cards at 24–48 hours after birth
- Cards shipped to NBS laboratories for testing
- Results reported to state health departments
  - Follow-up on positive screens
- The majority of state NBS programs do not follow children beyond the diagnosis phase

Anderson R, Rothwell E, Botkin JR. *Annu Rev Nurs Res*. 2011;29:113–32.

Point-of-Care Screening for Congenital Hearing Loss and CCHD

- Performed at the birthing facility before discharge
- Newborns not passing NBS are referred for diagnostic testing
- Point-of-care screening and reporting much less centralized than bloodspot screening
  - Challenges to collecting data for evaluation and monitoring
  - Difficulty ensuring diagnostic follow-up

Challenges with NBS in the United States (circa 2000)

- In mid-2000s, **extraordinary variation** from state to state
- Little **systematic evaluation of the rationale** for, and/or the outcomes of, screening
- In 2002, a national panel of experts began work on a **standard panel** of conditions for NBS


The Examiner.
WASHINGTON
Infant screenings come down to accident of birth
What side of the Potomac your baby is born on can determine how many tests it's given
Hope floats for children in need of love

US Department of Health and Human Services (HHS) Recommended Uniform Screening Panel (RUSP)

In 2005, HHS Secretary's **Advisory Committee on Heritable Disorders in Newborns and Children** (ACHDNC) proposed the RUSP **(29 conditions)**

- **20 conditions** are disorders of amino acids, fatty acids, and organic acids
  - Detected by a sophisticated laboratory technique (tandem-mass spectroscopy)
- 3 are **hemoglobinopathies** (types of sickle cell disease)
- 6 other conditions
  - Biotinidase deficiency
  - Congenital adrenal hyperplasia
  - Cystic fibrosis
  - Congenital hypothyroidism
  - Galactosemia
  - Hearing disorders

Updated RUSP

- Since 2005, 6 conditions added
  - Severe combined immunodeficiency (2010)
  - CCHD (2011)
  - Pompe disease (2015)
  - Mucopolysaccharidosis, type I (2016)
  - Adrenoleukodystrophy (2016)
  - Spinal muscular atrophy (2018)

Prevalence of RUSP Conditions in the United States

- Most conditions (except hearing loss) are **rare**
- Estimated annual number **(most common)**
  - Hearing loss: 6,337
  - Congenital hypothyroidism: 2,156
  - Sickle cell disease: 1,775
  - Cystic fibrosis: 1,248
  - Medium-chain acyl-CoA dehydrogenase deficiency (MCAD): 239
- Approximately **14,600** infants are diagnosed and treated each year with the RUSP core conditions

2016 Annual Data http://www.cdc.gov/ncbddd/hearingloss/ehdi-data2016.html

Impact of Expanded Newborn Screening—United States, 2006 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5737a2.htm

Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths. JAMA 2017;318:2111-2118.

Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK.; Baker, M.; Ballow, M.; Bartoshesky, L.E.; Bonagura, V.R.; et al. Newborn screening for severe combined immunodeficiency in
11 screening programs in the United States. JAMA. Netw. 2014, 312, 729–738

Process for Adding New Conditions to the RUSP

1. **Nomination** of a condition
   - ACHDNC reviews nomination to decide if there is sufficient evidence to proceed
     - Public health burden; valid screening test; confirmatory diagnostic test; population-based pilot studies
2. **Review** of the evidence
   - **Systematic review** of published and unpublished evidence
   - Decision analysis modeling of **benefits and harms**
   - Assessment of **readiness,** feasibility, and cost to state public health systems
3. ACHDNC **considers evidence and votes** whether to recommend condition
4. HHS Secretary considers ACHDNC recommendation and is the **final decision maker**

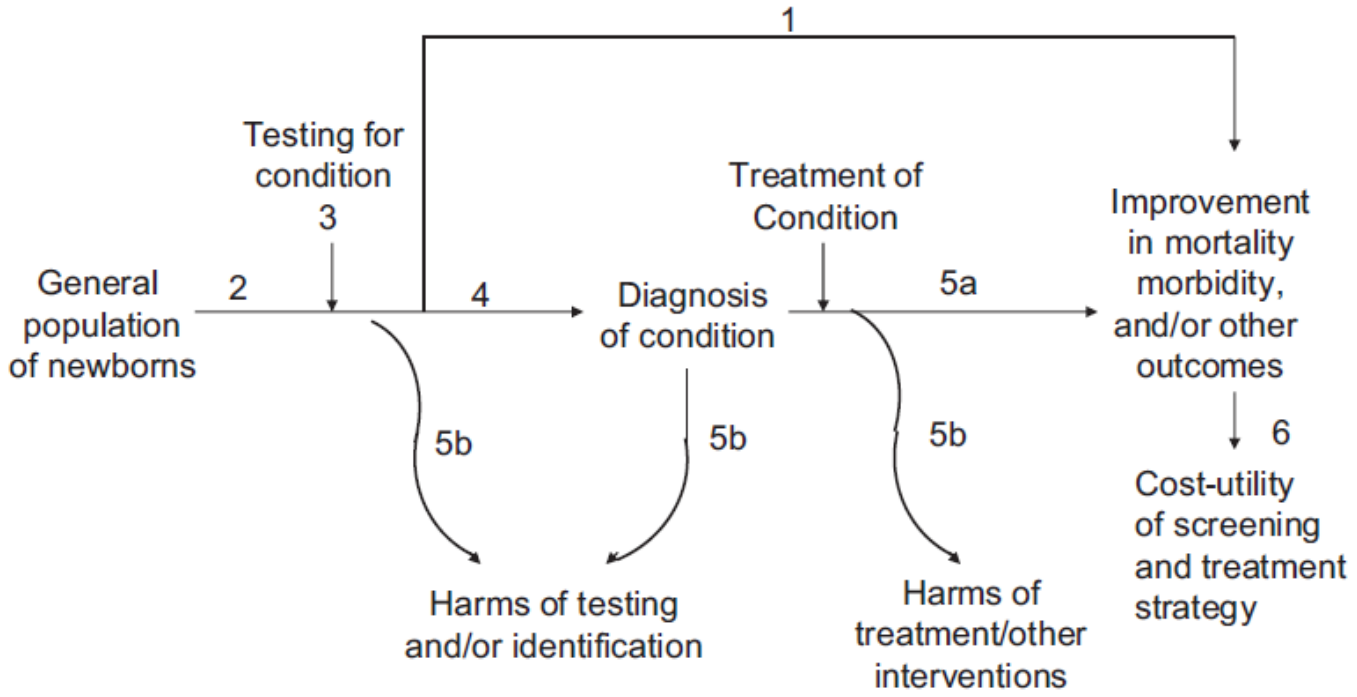
https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate.html

Criteria for Selecting Conditions for NBS

- **Magnitude of burden** of disease – incidence and severity
- Preclinical treatment **improves health outcomes**
- **Reliable screening test** that is feasible, acceptable, and affordable
  - Population-based pilot studies
- **Effective treatments** exist and are readily available
  - Consensus on who should be treated
- ***System in place*** for screening, diagnostic testing, counseling, and treatment

ACHDNC: Graphic of Analytic Framework for Evidence Review

Fig. 1. The analytic framework depicts the considerations of evidence for population-based screening of newborns for a specific important health condition (or set of conditions).



Adapted from U.S. Preventive Services Task Force Procedure Manual, http://www.ahrq. gov/clinic/uspstf08/methods/procmanual.pdf.

ACHDNC: Decision-making Process

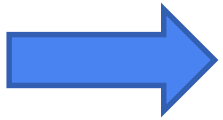
Table 1 Classification system used by the Advisory Committee

Net benefit to the population of newborns screened		States' capability to offer comprehensive newborn screening	
Rating	**Description**	**Rating**	**Description**
A	High certainty that screening for the targeted condition would lead to a significant net benefit	1	Screening has high to moderate feasibility[a] and most newborn screening programs are ready for comprehensive screening
B	Moderate certainty[b] that screening for the targeted condition would lead to a significant benefit	2	Screening has high to moderate feasibility and most newborn screening programs have developmental readiness for comprehensive screening
C	High or moderate certainty that screening for the targeted condition would lead to a small to zero net benefit	3	Screening has high to moderate feasibility and most newborn screening programs are unprepared for comprehensive screening
D	High or moderate certainty that screening for the targeted condition would lead to a negative net benefit	4	Screening has low feasibility
L	Low certainty regarding the net benefit of screening		

[a]High to moderate feasibility is based on the Advisory Committee's determination that there is an established and available screening test that can be adopted, a clear approach to diagnostic confirmation, and a treatment plan that is acceptable to clinicians and affected individuals and their families, and plans for long-term follow-up can be established.[b]Moderate certainty indicates that the Advisory Committee believes that further research could change the magnitude or direction of findings within any of the key questions such that the assessment of net benefit would be small to zero or even negative.

Kemper et al. Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: Statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genetics Med*. 2014: 16: 183-187.

ACHDNC Decision Matrix



Net benefit		Feasibility	Readiness		
			Ready	Developmental	Unprepared
Significant benefit	High certainty	High or moderate feasibility	**A1**	**A2**	**A3**
		Low feasibility	**A4**		
	Moderate certainty		**B**		
Zero to small benefit	High or moderate certainty		**C**		
Negative benefit			**D**		
	Low certainty		**L**		

Kemper et al. Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: Statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genetics Med*. 2014: 16: 183-187.

RUSP Decision-making Process

- HHS Secretary makes the decision after weighing the recommendations of the ACHDNC
- RUSP is a guideline
  - final decision is with the state; state-by-state process

Newborn Screening Criteria -- cCMV

Burden of cCMV Infection

- cCMV infection occurs in ~0.5% of infants based on a large US multi-center screening study using multiple methods
  - 20,000 newborns with cCMV infection in 4 million US births; few are diagnosed
  - cCMV is the leading viral cause of hearing loss in the United States
- Infection ≠ condition

Barkai G, Ari-Even Roth D, Barzilai A, et al. Universal neonatal cytomegalovirus screening using saliva - report of clinical experience. *J Clin Virol*. 2014;60(4):361-6.

Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A. Saliva polymerase-chain -reaction assay for cytomegalovirus screening in newborns. *N Engl J Med* 2011; 364: 2111–8.

cCMV Symptoms and Sequelae

- ~10-15% of infants with cCMV are symptomatic at birth
  - Clinical signs
    - jaundice, skin lesions or rash, liver or spleen enlargement, small head size (microcephaly), intrauterine growth retardation, and seizures
  - **Non-specific signs; many infants with symptoms never diagnosed**
- Long-term outcomes of symptomatic cCMV
  - Elevated risk of infant death: 5-10%
  - Disabling conditions in 50% of children (cerebral palsy, intellectual disability, sensorineural hearing loss, and eye problems)

Dreher AM, Arora N, Fowler KB, Novak Z, Britt WJ, Boppana SB, Ross SA. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. J Pediatr. 2014;164(4):855-9

Cannon MJ, Grosse SD, Fowler KB. Cytomegalovirus epidemiology and public health impact. In: *Cytomegaloviruses: From Molecular Pathogenesis to Intervention.* MJ Reddehase, ed. Norfolk, UK, Caister Academic Press. 2013. Volume II, pp. 26-48.

Alarcon A, Martinez-Biarge M, Cabanas F, et al. Clinical, biochemical, and neuroimaging findings predict long-term neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2013;163(3):828-34

Asymptomatic cCMV

- Major sequela in **asymptomatic** cCMV is sensorineural hearing loss (SNHL)
  - 15% with SNHL
    - By 12 months--5% with severe-profound loss
    - 900 children could benefit from early identification
  - 50-60% of cCMV SNHL can be detected through newborn hearing screening; others are late-onset or progressive HL
- **Most studies show no excess risk of intellectual disability**
  - However, some children without apparent symptoms may have experienced brain damage in utero

Cannon MJ, Grosse SD, Fowler KB. Cytomegalovirus epidemiology and public health impact. In: *Cytomegaloviruses: From Molecular Pathogenesis to Intervention.* MJ Reddehase, ed. Norfolk, UK, Caister Academic Press. 2013. Volume II, pp. 26-48.

Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: A quantitative assessment. *J Clin Virol*. 2008; 41(1):57–62.

Evidence of Late-onset and Progressive SNHL: Houston cCMV Longitudinal Study

- **During 1982-1992, 32,543 newborns underwent hospital-based screening by urine culture**
  - Cohort of 92 newborns with asymptomatic cCMV infection
    - No CMV-related symptoms
    - Long-term audiological follow-up for 86 children up to age 18, median 8 evaluations (range 2-17), 95% followed to 9+ years
  - Comparison group: 51 uninfected newborns, median 3 evaluations
  - SNHL ≥25 dB in any ear

Lanzieri TM, Chung W, Flores M et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. *Pediatrics.* 2017; 139:e20162610.

Cumulative Risk of SNHL

- Prevalence of SNHL assessed at various ages
  - **3 months:** 7% of case group vs. 0% of comparison group
  - **5 years:** 14% of case group vs. 0% of comparison group
  - **14 years:** 23% of case group vs. 8% of comparison group

Lanzieri TM, Chung W, Flores M et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 2017; 139:e20162610.

Implications of Findings

- Children with asymptomatic cCMV at increased risk of developing SNHL through age 5 years
  - Excess risk of SNHL relative to uninfected children about 15%

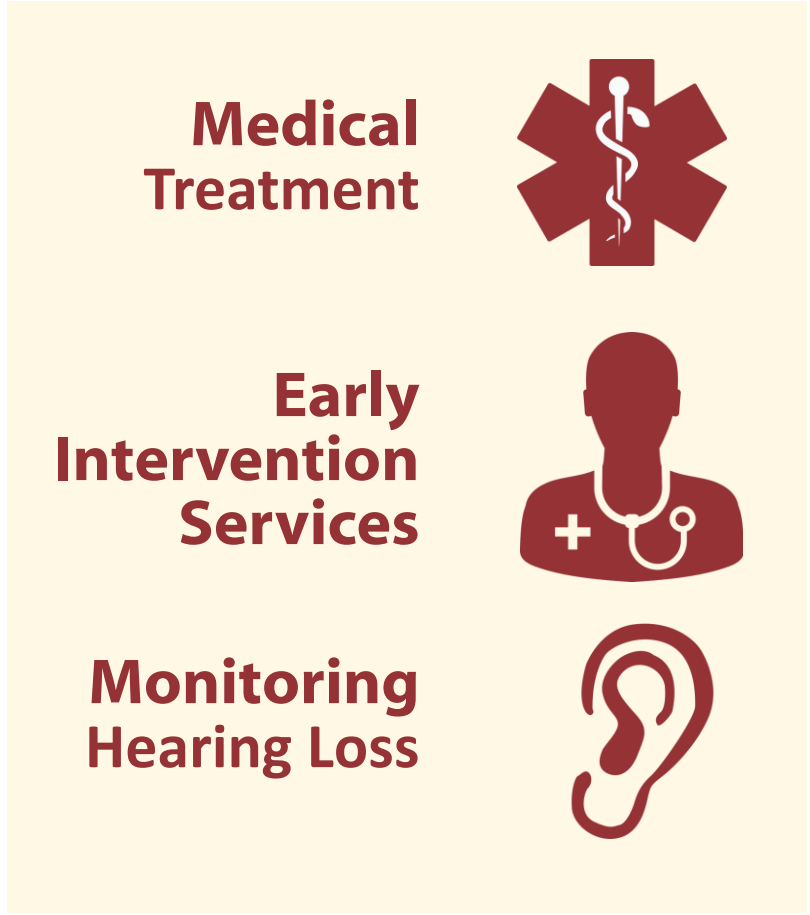
- SNHL is either late-onset or progressive in up to 50% of cases among children with asymptomatic cCMV
  - Newborn hearing screening may not detect ~50% of cases

Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. *Clin Infect Dis*. 2013;57 Suppl 4:S182-4.

Goderis J, De Leenheer E, Smets K, et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. *Pediatrics*. 2014;134(5):972-82.

Intervention and Treatment

- Medical treatment
  - Antiviral medications
  - Hearing amplification and cochlear implants
- Early intervention (EI) services
  - Developmental services
  - Hearing and language interventions
- Monitoring for late-onset and progressive hearing loss



Benefits and Harms of Antiviral Treatment

- **Benefits:** Good evidence of efficacy among infants with symptomatic cCMV with CNS involvement
  - reduced progression of hearing; significant language and communication outcomes; improved hearing
- Evidence lacking for other groups of infants with cCMV
- **Harms:** Transient neutropenia is common
- Due to toxicity concerns, recommendations for use focus on symptomatic infants with CNS involvement

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Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr.* 2003;143:16–25

Kimberlin DW, Jester PM, Sanchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015; 372:933–943.

Why Screen for cCMV? Potential Benefits

- **Primary target**: Identify asymptomatic infants at risk of SNHL
  - Enable monitoring for language development, hearing loss
  - Refer infants for early intervention therapies if SNHL is diagnosed
  - Prescribe antiviral treatment to those with possible SNHL?
    - Clinical trial in progress

- **Secondary target**: Identify infants with symptomatic cCMV, many missed
  - Initiate antiviral treatment ASAP
  - Refer for EI services

Sorichetti B, Goshen O, Pauwels J, et al. Symptomatic Congenital Cytomegalovirus Infection Is Underdiagnosed in British Columbia. *J Pediatr*. 2016 Feb;169:316-7.

Pickering LK, Baker CJ, Kimberlin DW, Long SS. Red Book. 29th edition of the Committee on Infectious Diseases, American Academy of Pediatrics. 2012

Swanson EC, Schleiss MR. Congenital cytomegalovirus infection: new prospects for prevention and therapy. *Pediatr Clin North Am*. 2013;60(2):335-49

Audiological Monitoring—
Late-onset or Progressive SNHL and cCMV

How often should asymptomatic children with cCMV be assessed for hearing loss?

- "Children with risk indicators that are highly associated with delayed-onset hearing loss, such as having received ECMO or having CMV infection, should have more frequent audiological assessment." *
- "Frequent audiologic monitoring at 6-month intervals until age 5 years should be strongly considered, with the possibility of more frequent monitoring every 3 months when hearing levels are changing or until the child is talking." **

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*Joint Committee on Infant Hearing. 2007 Position Statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics, 2007;120: 898-921.

**Fowler KB. Congenital cytomegalovirus infection: audiologic outcomes. Clin Infec Dis 2013; 57: S182-S184.

Impact of Early Hearing Diagnosis and Intervention

- Early intervention (<6 months) after NBS for hearing loss
  - Improves language development and reading comprehension
  - Lowers educational costs
- Fitting of cochlear implants for children with acquired severe SNHL (>70 dB) also improves outcomes
  - Children with late-onset SNHL who were fitted within 12 months have better speech and language outcomes

Yoshinaga-Itano C, Sedey AL, Wiggin M, Chung W. Early hearing detection and vocabulary of children with hearing loss. *Pediatrics* 2017; 140:e20162964.

Kennedy CR, McCann DC, Campbell MJ, et al. Language ability after early detection of permanent childhood hearing impairment. *N Engl J Med.* 2006;354:2131-41.

Pimperton H, Blythe H, Kreppner J, et al. The impact of universal newborn hearing screening on long-term literacy outcomes: a prospective cohort study. *Arch Dis Child*. 2016;101(1):9-15.

Schroeder L, Petrou S, Kennedy C, et al. The economic costs of congenital bilateral permanent childhood hearing impairment. *Pediatrics*. 2006;117:1101–12.

Grosse SD. Education cost savings from early detection of hearing loss: New findings. *Volta Voices*. 2007;14(6): 38-40.

Geers AE. Speech, language, and reading skills after early cochlear implantation. *Arch Otolaryngol Head Neck Surg* 2004;**130**:634–8.

Potential NBS Strategies for cCMV

- **Targeted** screening
  - cCMV testing of specimens collected <21 days for infants who do not pass newborn hearing screening
  - Targeted screening adopted as state policy in UT, CT, IA, and IL
- **Universal** screening - add cCMV to RUSP screening panel
  - Screening using already collected DBS sent to public health lab
  - Collection of new specimens (saliva) in birth hospital and transport to laboratory for testing

Dollard SC, Grosse SD, Schleiss MR. Newborn screening for congenital CMV. *J Inher Metabol Dis.* 2010; 33(Suppl 2):S249–254.

Grosse SD, Dollard S, Ross DS, Cannon M. Newborn screening for congenital cytomegalovirus: Options for hospital-based and public health programs. *J Clin Virol*. 2009; 46S:S32–S36.

Gantt S, Dionne F, Kozak FK, et al. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. *JAMA Pediat*r. 2016 Oct 10.

Opportunities to Build the Evidence

Criteria for Selecting Diseases for NBS

- **Magnitude of burden** of disease – incidence and severity ✓
- Preclinical treatment **improves health outcomes** ?
- **Reliable screening test** that is shown to be feasible, acceptable, and affordable ?
  - High sensitivity, high throughput, low cost
  - Population-based pilot studies
- **Effective treatments** exist and are readily available ?
  - Consensus on who should be treated
- **System in place** for screening and diagnostic testing, counseling, and follow-up ?

Building the Evidence for cCMV NBS

- More evidence is needed
  - Screening test methods for viral DNA
    - Accuracy of DBS assays in **high-throughput** testing
    - Feasibility and cost of testing saliva and urine specimens
  - Screening test – high sensitivity, ***high throughput, low cost***
  - Diagnostic test—high sensitivity and specificity, lower throughput, higher cost

- Population-based pilot studies preferably in the United States (ACHDNC requirement)

Saliva or DBS for cCMV Screening?

- Advantages of saliva
  - Saliva and urine currently specimens of choice to **diagnose** cCMV due to high viral load
  - Analytical sensitivity >90%

- Disadvantages of saliva
  - Lack of a existing system for ongoing collection and testing in state NBS labs
  - If hospital-based testing
    - generally **higher** cost**, less standardized** quality, and **lower** follow-up rates

Saliva or DBS for cCMV Screening?

- Advantages of DBS
  - DBS obtained on nearly **all newborns**
  - Reduce expense and enable **high-throughput testing**
  - May have **high clinical sensitivity** based on associations between high viral load and severity of disease
- Disadvantages of DBS
  - CMV viral load in blood 2-3 logs lower than in urine or saliva
  - Analytical sensitivity of DBS 30-80%, depending on lab methods
  - Clinical sensitivity of DBS unknown

CDC/Minnesota NBS Study to Establish Clinical Sensitivity of DBS for CMV Testing

- Enrollment Goal: 30,000 infants over 5 years
- Specimen Collection
  - Saliva swab for identification of all infected infants
  - DBS; already obtained for NBS
- Testing
  - Saliva swabs tested at UM lab within one week, results reported to PCP and parents
  - DBS specimens tested by CDC and UM labs
- Follow-up for CMV-positive infants
  - Annual review of medical records through age 4 years
  - Hearing tested every 6 months by MN EHDI Program, assessment of program's ability to handle influx of infants

Building the Evidence for cCMV NBS

- Benefits of **ongoing** audiological monitoring for cCMV positive babies
  - Who will perform audiologic assessments? Barriers to access
  - How often and how long should children be monitored?

- Agreement on who should be treated with antivirals
  - Outcomes of antiviral treatment in children without CNS involvement remain uncertain
  - RCT data needed–trials are planned/underway

Unique Aspects of NBS for cCMV

- **Large** asymptomatic group that will not develop disease/symptoms
  - Potential harms -- psychological stress for families with asymptomatic cCMV child
- **Long-term** follow-up cCMV **Program** – provide ongoing support and follow-up for families

Thank You for Listening

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For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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