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 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

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
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

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

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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
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).

Table 1 Classification system used by the Advisory Committee

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Rating</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>High certainty that screening for the targeted condition would lead to a significant net benefit</td>
<td>1</td>
<td>Screening has high to moderate feasibility and most newborn screening programs are ready for comprehensive screening</td>
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<td>B</td>
<td>Moderate certainty* that screening for the targeted condition would lead to a significant benefit</td>
<td>2</td>
<td>Screening has high to moderate feasibility and most newborn screening programs have developmental readiness for comprehensive screening</td>
</tr>
<tr>
<td>C</td>
<td>High or moderate certainty that screening for the targeted condition would lead to a small to zero net benefit</td>
<td>3</td>
<td>Screening has high to moderate feasibility and most newborn screening programs are unprepared for comprehensive screening</td>
</tr>
<tr>
<td>D</td>
<td>High or moderate certainty that screening for the targeted condition would lead to a negative net benefit</td>
<td>4</td>
<td>Screening has low feasibility</td>
</tr>
<tr>
<td>L</td>
<td>Low certainty regarding the net benefit of screening</td>
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</tbody>
</table>

\*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.\*\*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.

### ACHDNC Decision Matrix

<table>
<thead>
<tr>
<th>Net benefit</th>
<th>Feasibility</th>
<th>Readiness</th>
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<tbody>
<tr>
<td>Significant benefit</td>
<td>High or moderate feasibility</td>
<td>A1</td>
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<tr>
<td>Low feasibility</td>
<td>A2</td>
<td>A3</td>
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<tr>
<td>Moderate certainty</td>
<td>Ready</td>
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<td>Developmental</td>
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<tr>
<td></td>
<td>Unprepared</td>
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<tr>
<td>Zero to small benefit</td>
<td>B</td>
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<tr>
<td>Negative benefit</td>
<td>C</td>
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<tr>
<td>Low certainty</td>
<td>D</td>
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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

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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)


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


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

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

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

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


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

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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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


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

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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)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.