Newborn Screening for Neurodevelopmental Disorders

Wendy Chung, MD PhD
History of Newborn Screening

• Phenylketonuria (PKU) was the first disorder with population based screening in 1964 in Massachusetts
• Guthrie test (microbial inhibition assay)
• Hemoglobinopathies added in 1980’s after clinical trials showed that PCN prophylaxis was effective
Traditional Criteria for population screening

1) Important health problem
2) Accepted treatment
3) Diagnosis and treatment facilities available
4) Recognizable latent or early symptomatic state
5) Suitable test or examination
6) Test is acceptable to the population
7) Natural disease history adequately understood
8) Agreed policy on whom to treat as patients
9) The cost balanced relative to possible expense for medical care
10) Case finding is a continuous process

Wilson and Junger – WHO, 1968
Newborn Screen

• Population based screen of all newborns
• Financed and administered at the state level
• In NYS paid for taxpayers (public health law 2500a)
New Technologies in Newborn Screening

• Conversion to tandem mass spec
  • MCAD-medium chain acyl dehydrogenase
• Confirmation with DNA diagnostic tests
  • Cystic fibrosis (efficacy of early treatment?)
  • Measure immunoreactive trypsin
How is the Panel of Newborn Screening Tests determined?

- Public Interest
- Professional Interest
- Political Interest
- Cost Savings (Benefits Outweigh Costs)
- Scientific Evidence (Incidence/Outcome)
National Newborn Screening Guide

HRSA Contract With ACMG to Reevaluate the Traditional Criteria of Wilson and Junger

- Expert panel convened to review available information on newborn screening (NBS) and to make recommendations based on accumulation and analysis of best scientific evidence
- Task: To review policies and procedures and suggest equitable testing standards for state NBS program
- Deliverables:
  1) A model decision matrix for changing NBS screening panels.
  2) A uniform panel of conditions for screening.

Completed: December 2004
Criteria and Scoring System

- Incidence of conditions
- Identifiable at birth
- Burden of disease
- Availability of test
- Test characteristics
- Availability of treatment
- Cost of treatment
- Efficacy of treatment
- Benefits to individual
- Benefits to Fam. & Soc.
- Mortality prevention
- Diagnostic confirmation
- Acute management
- Simplicity of therapy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categories</th>
<th>Score</th>
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<tbody>
<tr>
<td>Incidence of conditions</td>
<td>&lt;1,000</td>
<td>100</td>
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<tr>
<td></td>
<td>1,000-25,000</td>
<td>75</td>
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<td>25,001-250,000</td>
<td>50</td>
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<td>&gt;250,000</td>
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<tr>
<td>Sign &amp; symptoms clinically identifiable in the first 48 hours</td>
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<td>100</td>
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<td></td>
<td>&lt;25% cases</td>
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<td></td>
<td>&gt;25% cases</td>
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<td></td>
<td>&gt;75% cases</td>
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<td>Burden of disease (Natural Hx If untreated)</td>
<td>Severe</td>
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<td></td>
<td>Moderate</td>
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<td></td>
<td>Minimal</td>
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<td>Does a sensitive and specific screening test ALC/GM/HAM currently exist?</td>
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<td>200</td>
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<td></td>
<td>No</td>
<td>0</td>
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<tr>
<td>Test characteristics (Yes = apply score, No = zero)</td>
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<td>Cost of treatment</td>
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<td>Potential efficacy of existing treatment</td>
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<td>Benefits of early intervention (INDIVIDUAL CRITICOM)</td>
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<td>Benefits of early identification (FAMILY &amp; SOCIETY)</td>
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<td>Early diagnosis and treatment prevent mortality</td>
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<td>Availability of diagnostic confirmation</td>
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<td>Acute management</td>
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<td>Simplicity of therapy</td>
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Main score 2100
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<th>Acylcarnitines</th>
<th>Amino Acids</th>
<th>Others</th>
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<td><strong>MS/MS</strong></td>
<td>OA</td>
<td>FAO</td>
<td>AA</td>
</tr>
<tr>
<td>Acylcarnitines</td>
<td>OA</td>
<td>FAO</td>
<td>Amino Acids</td>
</tr>
<tr>
<td>CPT-1B</td>
<td>OA</td>
<td>FAO</td>
<td>AA</td>
</tr>
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<td>CPT-1B</td>
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Average time for notification of initial screen-positive result

<table>
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<th>Days</th>
<th>%</th>
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<tr>
<td>4-7</td>
<td>12.5</td>
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<td>8-10</td>
<td>33.1</td>
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<td>11-14</td>
<td>16.2</td>
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<tr>
<td>15-21</td>
<td>14.5</td>
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<td>&gt;22</td>
<td>23.7</td>
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False positives

• Majority of positive results
• Usually due to mild transient elevations/depressions
  • PKU has 10:1 false:true positive ratio
  • Galactosemia is 50:1
  • CAH is 100:1
• Due to hyperalimentation/illness/liver dysfunction/prematurity
• Causes parental anxiety and increases expense of testing
What is an acceptable treatment outcome?

• Potential for normal outcome with simple intervention (MCADD)
• Potential for normal outcome with significant intervention (PKU)
• Potential for normal outcome, but probability of some disability (MSUD)
• Potential for better outcome, but certainty of disability (proprionic acidemia)
Secondary Costs

- Cost/anxiety of following up false positives
- Effect on parental bonding
- Assignment of a sick role for a well child
SPINAL MUSCULAR ATROPHY (SMA)

- A spectrum of neurologic disease caused by deletion or mutation within the survival motor neuron (SMN1) gene

- Rare, but it is one of the most common pediatric neuromuscular diseases

- Progressive, devastating, and fatal in its most severe form

Type 1

Type 2

Type 3
Newborn Screening for SMA

• Common autosomal recessive condition with incidence of 1/6400
• 98% of mutations are a single mutation
• Variability in severity due to SMN2 copy number and other unpredictable factors
• Degenerative condition
• Novel treatments, but may not work unless administered presymptomatically or in early stages of disease
SPINAL MUSCULAR ATROPHY (SMA) NEWBORN SCREENING
THE RESULT OF SMA NEWBORN SCREENING

14 months old
SEIZURES

SLC2A1 Gene
96,641 Live births in New York City in 2020

- White: 33.9%
- Hispanic: 28.9%
- Black: 23%
- Asian/Pacific Islander: 16.5%
- American Indian/Alaska Native: 0.1%
Community Advisory Council

- Parent representatives and our community advisory council were consulted for the gene list and study design

- Minimize burden
  - No additional sample

- Remote online consenting is acceptable

- Opportunity to consent up to one month after birth
GUARDIAN: Genomic Uniform-screening Against Rare Diseases In All Newborns

- 3rd Trimester Prenatal Recruitment
- Postnatal Consent
- Genomic Sequencing for 237 genes
- Clinical Result in Epic 3-6 weeks
- Early treatment to improve health outcomes
The GUARDIAN study is a free newborn screening study to help all babies have healthier lives.
Postnatal recruitment and consent

• Bilingual trained research assistant inviting new mothers after delivery  
  • Including mothers who have pre-consented
• Brochure and link to study video shared with mother
• CHOICE  
  • Group 1 only  
  • Group 1+2
• Electronic consent Option to talk with study GC by phone  
• Option to have consent emailed to them
Conditions Screened

• Condition list determined by:
  • Pediatric-onset
  • Actionability
  • Confirmatory testing available

Group 1 (all)
• 158 conditions (148 genes)
• Metabolic, Cardiac, SCID, Ophthalmologic
• Treatment (diet, medication, ERT, gene therapy)
• Confirmation testing

Group 2 (choice)
• 100 conditions (90 genes)
• Neurological conditions
• Behavioral interventions, seizure control
• Variable confirmation testing
Framework for including conditions

- Median age of onset before age 5 years
- Penetrance of core symptoms >90%
- Effective treatment for group 1 conditions (comparable to the effectiveness of treatments for core RUSP conditions)
- Well established natural history for group 2 conditions
- Average callability >99%
- Conditions were unanimously agreed upon after review by all stakeholders
- After evaluating the workload generated from the V1 list, plan to add at least 131 genes in V2 (125 group 1 conditions)
Methods

• Genome sequencing will be performed on the same DBS used for routine NBS, will take longer than routine NBS results

• DBS samples will be used for the majority of orthogonal confirmatory testing. CNV confirmation will require a buccal swab

• In silico filtering to restrict the analysis to genes for which consent has been given
  • No retrospective analysis if the gene list is modified
Comparison with traditional NBS

- Some conditions from the RUSP are technically challenging
  - Congenital Adrenal Hyperplasia
- Sensitivity of GS might be lower or higher than traditional NBS methods for some of the RUSP conditions
- The scope of GS is wider
- Higher positive predictive value is expected
- Both approaches are complementary
Group 1 conditions

• All have effective treatment
  • Diet or supplements
  • Oral medication
  • Infusion medication
  • Hearing aids
  • Gene therapy
  • Enzyme replacement treatment
  • Hematopoietic stem cell transplant
Parents have the choice at time of consent to have baby screened for Group 2 conditions

- 100 Neurogenetic disorders
  - Intellectual disabilities, autism, seizures
  - Natural history is well established

- Benefits of early diagnosis and implementation of developmental therapies

- Variable orthogonal testing
  - Mass spectrometry
  - Parental testing
Results

• Returned 3-6 weeks after specimen collection
• Integrate standard Newborn screening results with GUARDIAN results through study staff

Negative Screen
• Disclosed to participant via phone then email/mail
• Negative results sent to pediatrician via NBS system
• Results placed in EPIC
Pediatrician/Patient Support

- Full results in EPIC
- Positive results called out and emailed to pediatricians
- ACTion sheets with recommendations and guidelines
- FAQ on study website
- In person/ virtual genetic counseling and geneticist follow up appointments for all screen positive
- On call study genetic counselor
- Patient navigator and social worker
Long term goals

- Early diagnosis and treatment to improve the health of babies who participate in the study
- Generate evidence to support the expansion of NBS through genomic sequencing
- Characterize the prevalence and natural history of rare genetic conditions
Study Recruitment

- Eligible
  - Approached: 91%
  - Recruited: 71%

Mode of recruitment:
- In Person: 3%
- Remote: 97%

Preferences for conditions:
- Group 1: 87%
- Group 1 & 2: 13%

Preferred language:
- Group 1: 80% Spanish, 20% English
- Group 1 & 2: 80% Spanish, 20% English
Survey Follow-ups

I want to learn the results of the GUARDIAN study for my baby.

I wanted to help other babies who might benefit from better newborn screening.