Review of Newborn Screening & Updates

Traci McDermott, MD
November 22, 2013

Objectives

#1  Review of Newborn Screening and its’ national and local history
#2  The Numbers: Screening in Washington & Incidence of tested congenital disorders
#3  The importance of obtaining a second newborn screen & the research behind it
#4  Adding New Conditions to Recommended or Mandated Newborn Screening Panels & What’s New
#5  Overview of services provided by Department of Health Newborn Screening Services & available resources
What is *Newborn* Screening?

An integrated system that includes:

- Universal screening - all infants
- Follow-up to assure appropriate clinical response
- Diagnosis of affected infants
- Appropriate treatment and clinical care
- Evaluation of system effectiveness

Why is Newborn Screening Important?

- It prevents death and disability to affected infants by providing early treatment
- It benefits the public through savings in health care costs and institutional care
NBS Goal:

Correctly identify babies with congenital disorders and assure that they receive treatment as soon as possible.
History of Newborn Screening

Screening Begins in the States

As the effectiveness of the NBS test became known and advocates made the case, states around the nation began to institute mandatory newborn screening programs.

1963
- Massachusetts
- Oregon
- Delaware*
- Vermont**

1964
- Louisiana
- New Jersey
- New York

1965
- Alabama
- Alaska
- California
- Colorado
- Connecticut
- Florida
- Hawaii
- Idaho
- Illinois
- Indiana
- Iowa
- Kansas
- Maine
- Maryland
- Michigan
- Minnesota
- Missouri
- Montana
- New Hampshire
- Ohio
- Oklahoma
- Pennsylvania
- Rhode Island
- South Carolina
- Utah
- West Virginia
- Wisconsin

1966
- Georgia
- Kentucky
- New Mexico
- Texas
- Virginia

1967
- Arkansas
- Nebraska
- Nevada
- North Dakota
- Washington

1968
- Tennessee

1973
- South Dakota

1978
- Arizona

1980
- District of Columbia

1983
- North Carolina
- Wyoming

1985
- Mississippi

*Screening in these states was experimental.
**Vermont was the first state in which universal newborn screening was practiced.

McDermott 11/22/13
History of Screening in Washington

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DISORDERS ADDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>PKU - test available - voluntary</td>
</tr>
<tr>
<td>1967</td>
<td>Statute adopted, promotes screening</td>
</tr>
<tr>
<td>1976</td>
<td>Statute revised, MANDATES screening</td>
</tr>
<tr>
<td></td>
<td>DOH given authority to add conditions; rules adopted to carry out intent of statute</td>
</tr>
<tr>
<td>1978</td>
<td>Congenital hypothyroidism (CH)</td>
</tr>
<tr>
<td>1984</td>
<td>Congenital adrenal hyperplasia (CAH)</td>
</tr>
<tr>
<td>1991</td>
<td>Hemoglobinopathies (Hb)</td>
</tr>
<tr>
<td>2004</td>
<td>Biotinidase deficiency (BIO)</td>
</tr>
<tr>
<td></td>
<td>Galactosemia (GALT)</td>
</tr>
<tr>
<td></td>
<td>Homocystinuria (HCY)</td>
</tr>
<tr>
<td></td>
<td>Maple syrup urine disease (MSUD)</td>
</tr>
<tr>
<td></td>
<td>Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency</td>
</tr>
<tr>
<td>2006</td>
<td>Cystic fibrosis (CF)</td>
</tr>
<tr>
<td>2008</td>
<td>Amino acid (AA) disorders: 3</td>
</tr>
<tr>
<td></td>
<td>Fatty acid oxidation (FAO) disorders: 4</td>
</tr>
<tr>
<td></td>
<td>Organic acid disorders (OA): 8</td>
</tr>
</tbody>
</table>

Objective # 2

The Numbers: Screening in Washington & Incidence of tested congenital disorders
How is Newborn Screening Done?

- ~87,000 newborns are screened each year
- ~174,000 specimens are processed
- ~5,500 abnormal results
- (~2,100 false positives)
- Preventing death or disability in 170 - 210 babies/year

Annual WA NBS Numbers

2011 WA DOH Birth Data

<table>
<thead>
<tr>
<th>Facility</th>
<th>Hospital</th>
<th>Birth Center</th>
<th>Home</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Births</td>
<td>80,377</td>
<td>1,006</td>
<td>1,674</td>
<td>86,956</td>
</tr>
<tr>
<td>Percent</td>
<td>92.4 %</td>
<td>1.2 %</td>
<td>1.9 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attendant</th>
<th>Certified Midwife</th>
<th>Licensed Midwife</th>
<th>Other Midwife</th>
<th>All Midwife</th>
<th>Total Births</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Deliveries</td>
<td>7,484</td>
<td>2,404</td>
<td>113</td>
<td>10,001</td>
<td>86,956</td>
</tr>
<tr>
<td>Percent</td>
<td>8.6 %</td>
<td>2.8 %</td>
<td>0.1 %</td>
<td>11.5 %</td>
<td></td>
</tr>
</tbody>
</table>
2012
Newborn Screening Annual Report

86,180 Babies Screened
• 115 severe disorders (1 in 749 babies)
• 94 mild forms (1 in 917 babies)

209 Total disorders (1 in 412 babies)

1,244 Hemoglobin traits (1 in 69 babies)

Disorders Detected This Year

<table>
<thead>
<tr>
<th>3rd Quarter</th>
<th>2013</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>23,133</td>
<td>66,076</td>
<td>Hospitals, Birth Centers &amp; Home Births*</td>
</tr>
<tr>
<td>43,950</td>
<td>124,340</td>
<td>Specimens Tested (most infants have two newborn screens performed)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infants Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd Quarter</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>37</td>
</tr>
<tr>
<td>29</td>
</tr>
<tr>
<td>66</td>
</tr>
</tbody>
</table>

*Excludes babies born at Bremerton and Whidbey Island Naval hospitals
a Includes 2 infants with phenylketonuria (PKU), 2 infants with maple syrup urine disease (MSUD), and one infant with tyrosinemia type 1 (TYR-1)
b Infant with medium chain acyl-CoA dehydrogenase (MCAD) deficiency
c Includes one infant with isovaleric acidemia (IVA), and one infant with methylmalonic acidemia (MMA), but excludes two infants with 3-methylcrotonyl CoA carboxylase (3-MCC) deficiency (a condition not on our mandatory screening panel)
Objective # 3

The importance of obtaining a second newborn screen & the research behind it

Timing is Critical

- Day 1 - Baby born at a local birthing hospital (< 25 miles from lab) NBS specimen collected at 26h
- Day 3 - Patient was admitted at tertiary hospital because of high blood ammonia levels
- Day 4
  - Received a call from a metabolic specialist inquiring about NBS results - specimen not received in NBS lab
  - Specimens sent via courier to Seattle Children’s lab confirming diagnosis of Propionic Acidemia
  - Patient underwent dialysis
- Day 5 - NBS specimen received, STAT testing revealed elevated C3 (propionyl carnitine)
- Day 8 - recovered from metabolic crisis
Benefits of the 2nd Newborn Screen

- Identify conditions that may not be evident in the first 48 hrs
- Identify mild forms of conditions on the NBS panel
- Rule out conditions on the NBS panel
  - Cutoffs are tailored on the 1st screen to reduce the # of borderline abnormal results & unnecessary referrals (decrease false positives)
- Resolve interfering substances (e.g. mom’s levels, administered medications)
- Confirm disease/trait – without need for further testing in some cases

<table>
<thead>
<tr>
<th>Amino Acid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argininosuccinic aciduria (ASA)</td>
</tr>
<tr>
<td>Citrullinemia (CIT)</td>
</tr>
<tr>
<td>Homocystinuria (HCY)</td>
</tr>
<tr>
<td>Maple syrup urine disease (MSUD)</td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
</tr>
<tr>
<td>Tyrosinemia type 1 (TYR-1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fatty Acid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnitine palmitoyl transferase deficiency (CPTD)</td>
</tr>
<tr>
<td>Long-chain acyl-CoA dehydrogenase (LCHAD) deficiency</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency</td>
</tr>
<tr>
<td>Tri saturated (TIPS) deficiency</td>
</tr>
<tr>
<td>Very long chain Acyl-CoA dehydrogenase (VLCAOD) deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organic Acid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-hydroxy-3-methylglutaryl aciduria (HMG)</td>
</tr>
<tr>
<td>Beta-oxidation (BO) deficiency (BO)</td>
</tr>
<tr>
<td>Citrinic aciduria (CIT)</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MSUD) and methylcitric acidemia (MCAD)</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency (MCCD)</td>
</tr>
<tr>
<td>Propionic acidemia (PAOP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital adrenal hyperplasia (CAH)</td>
</tr>
<tr>
<td>Congenital hyperinsulinism (CH)</td>
</tr>
<tr>
<td>Cystic fibrosis (CF)</td>
</tr>
<tr>
<td>Galactosemia (GALT)</td>
</tr>
<tr>
<td>Hemoglobinopathies (Hb)</td>
</tr>
</tbody>
</table>
2nd Screen & Adrenal Hyperplasia

- Sensitivity is increased
  - 73% sensitivity with 1 screen in Wisconsin Study – 2005
- False Negatives are reduced
  - 22% false negatives with 1 screen in Minnesota Study - 2012

### Congenital Adrenal Hyperplasia (CAH)

<table>
<thead>
<tr>
<th></th>
<th>Salt Wasting</th>
<th>Simple Viralizing</th>
<th>Non Classical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAH cases</td>
<td>42 (71%)</td>
<td>13 (24%)</td>
<td>3 (5%)</td>
<td>58</td>
</tr>
<tr>
<td>Total # screened</td>
<td>1: 19,000</td>
<td>1:58,000</td>
<td>1:270,000</td>
<td>809,849</td>
</tr>
<tr>
<td>False Negative on 1st NBS</td>
<td>8 (19.0%)</td>
<td>10 (76.9%)</td>
<td>---</td>
<td>18 (33%)</td>
</tr>
<tr>
<td>Overall False Negative</td>
<td>1a (2.3%)</td>
<td>1b (7.1%)</td>
<td>---</td>
<td>2 (3.6%)</td>
</tr>
</tbody>
</table>

10 year review of CAH Data from Washington State Department of Health
a 724g baby, 17OHP=53.5 on the 1st NBS and was on steroid treatment for 2nd NBS (17OHP=23.26)
b 3941g baby, 17OHP=25.16 on the 1st NBS and did not have a routine 2nd NBS
Effect of Laboratory Practices on the Incidence Rate of Congenital Hypothyroidism
Vicki Hertzberg, PhD, Joanne Mei, PhD, Bradford L. Therrell, PhD

“... laboratories that used a TSH assay for initial screening reported a 24% higher incidence rate of CH than those that used a T4 assay.”

Screening for Congenital Hypothyroidism With Specimen Collection at Two Time Periods: Results of the Northwest Regional Screening Program
Stephen H. LaFranchi MD, et al.

“... a routine second specimen led to an added detection rate of infants with hypothyroidism”

“... even very mild cases of congenital hypothyroidism which escape clinical diagnosis are at risk for neurologic damage.”
Screening Practices for Congenital Hypothyroidism

<table>
<thead>
<tr>
<th>State</th>
<th>Method / Cutoff</th>
<th>2nd Screen</th>
<th>Detected by 2nd Screen</th>
<th># Infants / Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>TSH ≥100</td>
<td>No</td>
<td>- - -</td>
<td>275</td>
<td>1: 2,200</td>
</tr>
<tr>
<td>Oregon</td>
<td>T4&lt;5; TSH&gt;25</td>
<td>Yes</td>
<td>33%</td>
<td>25</td>
<td>1: 2,000</td>
</tr>
<tr>
<td>Idaho</td>
<td>T4 &lt;5; TSH&gt;25</td>
<td>Yes</td>
<td>42%</td>
<td>12</td>
<td>1: 2,000</td>
</tr>
<tr>
<td>Washington</td>
<td>TSH≥15</td>
<td>Yes</td>
<td>33%</td>
<td>65</td>
<td>1:1,300</td>
</tr>
</tbody>
</table>

“... after adjusting for screening methodologies and parameters, an increasing incidence rate still persisted.”

2nd Screen & Hypothyroidism

<table>
<thead>
<tr>
<th>Classification</th>
<th>1st Screen</th>
<th>Subsequent Screen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumptive</td>
<td>41</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>Borderline</td>
<td>8</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>49 (67%)</strong></td>
<td><strong>24 (33%)</strong></td>
<td><strong>73</strong>*</td>
</tr>
</tbody>
</table>

2010 Data from Washington State Department of Health
Picking up True Positive Cases on the 2nd Screen: **Homocystinuria**

- 4121g baby girl
- **1st screen at 69 hrs of life:** Methionine = 64 µmol/L
  - cutoff at the time was 80 µmol/L, now it would be < 72 µmol/L
- **2nd screen at 15 days of life:** Methionine = 257 µmol/L
  - cutoff at the time was 80 µmol/L, now it would be < 72 µmol/L
- Diagnostic tests confirmed baby has Homocystinuria:
  - Methionine = 490 µmol/L (blood drawn 14 days after 2nd NBS)
  - non-responsive Vitamin B deficiency
  - baby on formula and doing well clinically
  - baby has never been symptomatic; normal physical and mental development

Picking up True Positive Cases on the 2nd Screen: **MCADD**

- 2780g baby boy
- **1st screen at 55 hrs of life:** C8 = 0.08; C10:1 = 0.07; C8/C10 ratio = 0.79; C8/C2 ratio = 0.01; all normal results
  - note: baby was in the NICU and on antibiotics, HA/TPN, and steroids
- **2nd screen at 8 days of life:** C8 = 0.72; C10:1 = 0.25; C8/C10 ratio = 2.23; C8/C2 ration = 0.06
- Diagnostic labs confirmed MCAD deficiency:
  - Abnormal organic acids and abnormal acylcarnitine profile
  - Genotyping: Y67H/G267R (199T>C/799G>A)
- Baby on formula
So why the 2\textsuperscript{nd} Screen?

- Two Screens, the 2\textsuperscript{nd} between 7-14 days is \textbf{standard of care*} in Washington, with >90% of infants having both screens performed
- We pick up 1/3 of one of the most common congenital conditions (CH) on the 2\textsuperscript{nd} Screen, avoiding significant developmental & growth delays
- Offers parents & the child’s medical provider increased reassurance that these conditions have been detected (increased sensitivity)

Objective # 4

Adding New Conditions to Recommended or Mandated Newborn Screening Panels & What’s New
Adding New Condition:
- Criteria for screening

- Early identification benefits the newborn
- Treatment is available
- Nature of the condition justifies population-based screening
- A good screening test exists
- The benefits justify the costs of screening

SCID – “The Bubble Boy”
Severe Combined Immunodeficiency

- Babies born with SCID lack immune cells, lymphocytes
- Early detection can avoid severe infections & prevent deaths
- With stem cell transplant, children can be ‘cured’

David Vetter, Baylor College of Medicine Archives
2014 New Screening Addition

- 2010: SCID recommended nationally by HHS
- 2012: WA Newborn Screening Committee approved
- October 9, 2013: State Board of Health Meeting - unanimous approval to add SCID to Washington’s required screening
- WAC 246-650-020 newborn screening rule will be revised to reflect this
- January 1, 2014: planned implementation

*Test done on same collected dried blood spot

Costs of Screening

- $60.90 – per baby (2012 and current)
- $69.00 – per baby (post SCID implementation)
- Plus $8.40 per baby to help support clinic care
Critical Congenital Heart Disease (CCHD) – Pulse Oximetry Screening

“The goal... is to identify newborns with structural heart defects usually associated with hypoxia in the newborn period that could have significant morbidity or mortality early in life with closing of the ductus arteriosus or other physiologic changes...”

Kemper AR et al Pediatrics 2011

- Added to the recommended universal screening panel in 2012
- Adopted by the AAP in Jan 2013
- More Later Today...
  - Amy Schultz, MD

Objective # 5

Overview of services provided by Department of Health Newborn Screening Services & available resources
"The Newborn Screening Story:
How one simple test changed lives, science and health in America"
Learning Outcomes

- Participants will be able to provide information to their colleagues regarding the disorders screened for by Washington State’s newborn screening program and those that have been universally recommended and adopted by many state hospitals.
- Participants will be able to discuss the incidence of disorders identified by newborn screening in relation to the percentage of births attended by midwives and infants born outside of hospitals in Washington State.
- Participants will be able to inform parents of the importance of newborn screening and how screening is conducted in Washington State.

References & Acknowledgement


Special Thanks to Mike Glass, Director of NBS