Overview of Newborn Screening: NICHD

Melissa Parisi - Tiina Urv
“The Secretary, in conjunction with the Director of the National Institutes of Health and taking into consideration the recommendations of the Advisory Committee, may continue carrying, and expanding, and to be known as...”

“Hunter Kelly Newborn Screening Research Program”
Goals of the Hunter Kelly Newborn Screening Research Program

- Identify, develop and test the most promising new screening technologies

- Increase the specificity of newborn screening and expand the number of conditions for which screening tests are available

- Develop experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and/or functional conditions that can be detected through newborn screening for which treatment is not yet available.
Identify, develop and test the most promising new screening technologies

Development of efficient and effective screening strategies for Lysosomal Storage Disorders, Friedreich ataxia, Wilson disease, and X-linked Adrenoleukodystrophy
Dieter Matern, MD – Mayo Clinic HHSN275201 0000 17C

<table>
<thead>
<tr>
<th>Method</th>
<th>Multiplex</th>
<th>Platform</th>
<th>Complexity</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Assay</td>
<td>No</td>
<td>Fluorometry</td>
<td>Low</td>
<td>?</td>
</tr>
<tr>
<td>Multiplex Enzyme</td>
<td>Yes</td>
<td>MS/MS</td>
<td>High</td>
<td>?</td>
</tr>
<tr>
<td>Multiplex Immune-Quantification Assay</td>
<td>Yes</td>
<td>Luminex</td>
<td>Low</td>
<td>??</td>
</tr>
<tr>
<td>Digital Microfluidics</td>
<td>Yes</td>
<td>“Lab-on-a-chip”</td>
<td>Low</td>
<td>??</td>
</tr>
</tbody>
</table>
Increase the specificity of newborn screening and expand the number of conditions for which screening is available.

**Newborn Screening for Spinal Muscular Atrophy and Duchenne/Becker Muscular Dystrophy**

Steven F. Dobrowolski, PhD – University of Utah

Amplify a homologous region of exon 7 from both SMN1 and SMN2 including c.840 where a “C” is present in SMN1 and a “T” is present in SMN2.

Melt profiling dye is included in the reaction and a pair of self-complementary oligos to create an invariant “calibrating” melt signal.

![SMA Profile](image)
Develop experimental treatments and disease management strategies…

- **Innovative Therapies and Tools for Screenable Disorders PAR**

  - Collaboration with NINDS, NIDDK and NIDCD
    - First issued in 2005
    - expires 9/2013

    - PAR-10-230 – R01
    - PAR-10-231 – R03
    - PAR-10-232 – R21
Sample of Funded Projects

- Gene Therapy for **Usher Syndrome** (USH1C)
- Anaplerotic therapy in **Propionic Acidemia**
- Novel Pharmacological Strategies for Liver Disease in **Antitrypsin Deficiency**
- Gene Therapy for Neurodegenerative **Lysosomal Storage Diseases**
- Gene Therapy of **Mucopolysaccharidosis VII**
- Development of Chemical Chaperonin for **Medium Chain Acyl-CoA Dehydrogenase Deficiency**
- Therapy of Neuronopathic **Gaucher Disease**
- Innovative Therapies and Clinical Studies for **Classic Galactosemia**
- Novel Therapies for **Globoid-Cell Leukodystrophy**
- Novel Treatment and Screening Strategies in **Heritable Gamma-Hydroxybutyric Aciduria**
- Cooperative lead development program for treatment of **Spinal Muscular Atrophy**
- Novel Therapy for a **Human Glycosylation Disorder**
- A preclinical trial of intratympanic antivirals for **CMV-related hearing loss**
- Mechanisms for immune tolerance in **Pompe Disease**
- Oral tolerance in enzyme replacement therapy of **Morquio A disease**
- Pharmacologic Chaperone Therapy in **Murine Gaucher Disease**
RFA - Natural History Studies

- **Pilot Newborn Screening Project for Identification and Prospective Follow-up of Infants with Spinal Muscular Atrophy**
  - Kathy Swoboda – University of Utah

- **Inborn Errors of Metabolism Collaborative: Defining the Natural History of Inborn Errors of Metabolism**
  - Cynthia Cameron – Michigan Public Health Institute
## State-wide Screening Pilots – Classic SCID and SCID Variant

<table>
<thead>
<tr>
<th>State</th>
<th>Start of Screening</th>
<th>Number of Months Screening</th>
<th>Annual Births or Number Studied</th>
<th>Number of Infants Screened as of April 30, 2011</th>
<th>SCID&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SCID Variant&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Non SCID&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>WI</td>
<td>1/1/2008</td>
<td>40</td>
<td>69,232</td>
<td>243,707</td>
<td>4</td>
<td>0</td>
<td>7</td>
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<tr>
<td>MA</td>
<td>2/1/2009</td>
<td>27</td>
<td>77,022</td>
<td>161,707</td>
<td>1</td>
<td>0</td>
<td>14</td>
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<tr>
<td>Navajo Nation</td>
<td>2/1/2009</td>
<td>27</td>
<td>2,000</td>
<td>1,297</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NY</td>
<td>9/30/2010</td>
<td>7</td>
<td>236,656</td>
<td>136,635</td>
<td>4</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>CA</td>
<td>8/1/2010</td>
<td>9</td>
<td>510,000</td>
<td>358,000</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>8/1/2010</td>
<td>9</td>
<td>45,620</td>
<td>29,115</td>
<td>0*</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>LA</td>
<td>10/1/2010</td>
<td>7</td>
<td>65,268</td>
<td>31,464</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Total</td>
<td>126</td>
<td>1,005,798</td>
<td>961,925</td>
<td></td>
<td>14</td>
<td>6</td>
<td>40</td>
</tr>
</tbody>
</table>
Emerging Findings

- Zero TREC with normal copy number for genomic PCR control consistently means the infant has profound T-cell lymphocyte deficiency
- Discovery that biomarker identifies two different clinically relevant populations
  - No TREC and Low TREC
- Initiation of newborn screening for a new disorder does contribute to clinical and scientific understanding, and facilitates new research questions
  - Emerging evidence regarding molecular etiology, incidence
- Incidence is generally higher than previously reported

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID, SCID Variant</td>
<td>1 in 34,000</td>
<td>1 in 29,582</td>
</tr>
</tbody>
</table>

*LA has not had a case*
Model of Collaboration Across HHS Agencies

**CDC**
Initial Pilots,
Quality Control and
Improvement
Materials to Insure
Accurate Tests

**HRSA**
Clinical Decision
Support Tools (ACT
Sheets) Guiding
Infants’ Health Care
Providers

**NIH NICHD**
Expanded Pilots and
Databases Enabling
the Diagnosis,
Treatment and Long-
Term Follow-up of
SCID Cases

HHS
...and now for a quick word from our sponsor.
Things to remember when thinking about the “Next Generation” of the NBSTRN

- The NBSTRN is funded through an NIH contract (not grant).
  - As an NIH project, the primary focus of all activities must be research.
  - Contracts by nature have more federal oversight than grants
    - READ: More rules and regulations to contend with
  - All activities need to stay within the scope outlined in the statement of work of the contract.
Focus of Newborn Screening at the NIH

- Identify, develop and test the most promising new screening technologies
- Increase the specificity of newborn screening and expand the number of conditions for which screening tests are available
- Develop experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and/or functional conditions that can be detected through newborn screening for which treatment is not yet available.
Statement of work for the NBSTRN

- Establish an organized network of State newborn screening programs and clinical centers
- Develop, implement and refine a national research informatics system for investigators and policy makers that dovetails with the established national clinics network
- Establish and administer an efficient and reliable virtual repository of residual dried blood spots comprised of those stored by State NBS programs and other resources.
- Provide expertise and support to researchers related to regulatory requirements associated with informed consent, IRBs and state and local research policy associated with NBS.
- Facilitate research on the development of new methods and technologies by maintaining close contact with the scientific and biomedical research communities.
Statement of work for the NBSTRN

- Facilitate research on screened and treated patients to define effectiveness of treatments and long-term outcomes
- Provide statistical leadership and clinical trial design expertise for the individualized needs of researchers
- Facilitate the timely dissemination of research findings
- Establish a steering committee comprised of knowledgeable healthcare professionals, public health professionals, ethicists and scientists to make recommendations to NIH program regarding research proposals to have access to NBSTRN
- NIH-supported researchers, in conjunction with their Institutes program officer, will nominate research projects for consideration by the network in order to gain access to the NBSTRN
Thank you for your hard work on this project!