Translational Research in Newborn Screening: Efforts to Facilitate Implementation of Newborn Screening for Severe Combined Immune Deficiency (SCID)

Michele Caggana, ScD presenting for Amy Brower, PhD and Fred Lorey, PhD
May 8, 2013
Nomination and Evidence Review Process

Nomination Form → Federal Administrative Review

AC Recommendations:
- Universal NBS
- Targeted screening
- Pilot study
- Critical studies needed
- No

Advisory Committee (AC)

Evidence Work Group

Further Study(ies)

10 Nominations
2 Approvals

Refer to the HHS Secretary
Recommendation to add SCID in January 2010 and endorsed by HHS Secretary in May 2010

Outlined the following activities

- Education and Training Materials - The Health Resources and Services Administration [HRSA]
- Quality Assurance - The Centers for Disease Control and Prevention [CDC]
- Expanded Pilots - The National Institutes of Health [NIH]
Key Components of Pilot

- Pilot in High Number Birth States
- High Capacity Assay Development
- Regionalization Model
- CDC Quality Assurance Program
- SCID R4S Data Portal
- NBSTRN Administrative Core
Expansion of SCID Newborn Screening Pilots

- NICHD initiated project to enable increased pilot screening – contract to NYS held by K. Pass, PhD extended

- Key Features
  - Initiates pilots in high number birth states (New York, California)
  - High capacity assay development (New York, California)
  - Regionalization model
    - Puerto Rico → Massachusetts
    - Louisiana → Wisconsin
  - CDC quality assurance program
  - Utilize NBSTRN
    - SCID data portal – analytical validation
    - Long-term Follow-Up
    - Monthly conference calls to share expertise
NBSTRN Scope of Work

Networks
- Clinical specialists
- State laboratories
- Federal partners
- Advocates and patients

Informatics
- Laboratory Performance Tool (R4S)
- Virtual Repository of Dried Blood Spots (VRDBS)
- Longitudinal Pediatric Data Resource (LPDR)

Facilitate Research
- Natural history studies
- Novel screening technologies
- Novel therapies
- Genomics

Focus
- Ethical, legal and social issues
- Study planning
- Data aggregation and discovery
- Statistics
R4S
- Analytical and clinical validation
- Laboratory protocols, definitions

VRDBS
- Search and request de-identified residual dried blood spots
- Secure research support and request management

LPDR
- Secure, standards-based clinical data collection and management
- Aggregate, share, and analyze data

Stakeholder Engagement
- Facilitate communication between experts and key stakeholders
- Monthly conference calls
Disseminate Pilot Findings

SCID Resources

Statement of Work for National SCID Pilot Study

Frequently Asked Questions: Newborn Screening for Severe Combined Immunodeficiency (SCID) Information for Parents

What is newborn screening?

Newborn screening is a procedure designed to identify infants with certain diseases, which would not usually be detected at birth. Early diagnosis and treatment of these diseases can prevent severe complications.

What is severe combined immunodeficiency?

SCID is an inherited disorder that affects the immune system. MCID patients have an immune system that does not work well. The immune system helps the body fight infections. Therefore, children with SCID have an increased risk of developing serious infections. They usually do not have a healthy normal immune system.

How does New York State screen for SCID?

Newborn screening for SCID involves a blood test to measure the level of T-cells, a type of white blood cell that helps fight infections. This test is performed on a blood sample taken from the baby's heel. If the test results are abnormal, additional testing may be needed.

My baby had a positive newborn screen for SCID. Does my baby definitely have SCID?

A positive newborn screen does not mean that your baby definitely has SCID. However, it means that additional testing is needed to confirm the diagnosis. Additional testing may include further blood tests or genetic testing. It is important to receive a second opinion before making a diagnosis.

How do I find out if my baby has SCID?

If your newborn screening test results are positive, your baby will need additional testing to confirm the diagnosis. This testing may include blood tests, genetic tests, or other diagnostic procedures. It is important to consult with a pediatrician or a specialist to determine the best course of action.

What is the treatment for SCID?

Children with SCID are treated with a combination of medications, vaccines, and other therapies. The goal is to provide the best possible care to help them live as normal a life as possible. This may include regular check-ups, medications, and other treatments.

Do you have a family history of SCID or other immunodeficiency disorders?

If you have a family history of SCID or other immunodeficiency disorders, it is important to discuss this with your healthcare provider. This may include genetic testing or counseling to identify any risks for your family members.

Who can I call if I have additional questions about newborn screening for SCID?

For more information or to obtain a screening form, you can call the Newborn Screening Program at 1-800-352-5764 or visit their website at www.nyscreening.org.
Continued Efforts to Facilitate Implementation of SCID NBS

- **Disseminate Pilot Findings and Resources**
  - Statement of Work for National SCID Pilot Study
  - Protocols and Algorithms
  - Support the R4S SCID Data Portal

- **Newer and Continuing Efforts**
  - Monthly Stakeholder Calls
  - Expansion of R4S SCID Data Portal (e.g. participants and capability)
  - Longitudinal Data Collection
  - Inclusion of Families and Advocacy Groups
  - Work with PIDTC and Other Partners
Newborn Screening Translational Research Network

Disseminate Established Resources

- Immune Deficiency Foundation Parent Brochure on SCID Customizable brochure for positive newborn screen.

- SCID Parents Guide for Positive Diagnosis

Newborn Screening for Severe Combined Immunodeficiency and Conditions Associated with T Cell Lymphopenia

What Does An Abnormal Screening Test Mean?
The screening test shows that your baby has low numbers of a type of white blood cell called CD4+ T cells. Low numbers of CD4+ T cells are associated with a group of disorders called Severe Combined Immunodeficiency (SCID). If you have low CD4+ T cells, your baby is more likely to have an abnormal screening test.

What is SCID?
SCID is a severe genetic disorder that affects a baby's immune system. When a baby's immune system is not developed properly, they can't fight off infections. As a result, babies with SCID are more likely to get sick and need medical care.

What Other Immune System Problems Could My Baby Have?
Conditions like SCID can affect a baby's immune system in different ways. For example, some babies with SCID may have higher levels of antibodies than normal, which can cause long-term health problems. Other babies with SCID may have low levels of antibodies, which can cause infections.

How Common is SCID?
In the United States, about 1 in 50,000 babies are born with SCID. Fortunately, most newborns with SCID can be identified through newborn screening programs. The National SCID Initiative has helped to reduce the number of newborns with SCID by identifying them early and offering及时 medical care.

How are SCID and Other Conditions Associated with T Cell Lymphopenia Diagnosed?
The most effective treatment for SCID is to provide frequent antibiotic therapy. However, many babies with SCID can benefit from antiviral therapy, which can help prevent infections.

A Guide for Parents Following a Diagnosis

Newborn Screening Translational Research Network
Massachusetts State Newborn Screening Program Brochures:
- Newborn Screening in Massachusetts: Answers for You and Your Baby

Wisconsin State Newborn Screening Program Brochures:
- Just a Few Drops of Blood...Can Detect Serious Hidden Disorders in Your Baby

Newborn Screening Translational Research Network
R4S
• Analytical and clinical validation
• Laboratory protocols, definitions

VRDBS
• Search and request de-identified residual dried blood spots
• Secure research support and request management

LPDR
• Secure, standards-based clinical data collection and management
• Aggregate, share, and analyze data

Stakeholder Engagement
• Facilitate communication between experts and key stakeholders
• Monthly conference calls
Monthly Conference Calls

Sample Standing Agenda

- Introduction of New Participants
- Implementation Status Review and Stakeholder Reports
- Effort to Report on National Experience
- CDC Update
- IDF Meeting
- Resources and Tools
- Submitted Discussion Items
- Discussion
- Number of participants steadily growing
- Number of states steadily growing
- Participant stakeholder groups
  - Newborn Screening Translational Research Network
January 2012 Update

Newborn Screening Translational Research Network

<table>
<thead>
<tr>
<th>Number of States</th>
<th>Shading</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>🟦</td>
<td>State-wide Screening</td>
</tr>
<tr>
<td>3</td>
<td>🟢</td>
<td>Partial Screening</td>
</tr>
<tr>
<td>16</td>
<td>🟢</td>
<td>Screening approved</td>
</tr>
<tr>
<td>22</td>
<td>🟣</td>
<td>Fact Finding</td>
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March 2013 Implementation Status

Newborn Screening Translational Research Network

- (12) Screening
- (2*) Selected populations
- (13) Pilots/Screening in 2013
- (24) Not Screening
<table>
<thead>
<tr>
<th>Selected Stats</th>
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<tbody>
<tr>
<td><strong>Total Number of Newborns Screened by 12/31/12</strong></td>
</tr>
<tr>
<td><strong>Percentage of Births Screened</strong></td>
</tr>
<tr>
<td><strong>States Planning Pilots or Screening in 2013</strong></td>
</tr>
<tr>
<td><strong>Estimated Percentage of Births Screened by 2014</strong></td>
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<tr>
<td><strong>Clinically Diagnosed Cases Since RUSP Addition in Non-screening States</strong></td>
</tr>
</tbody>
</table>

Newborn Screening Translational Research Network
R4S
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Stakeholder Engagement
- Facilitate communication between experts and key stakeholders
- Monthly conference calls
Laboratory Performance Tools

Co-curators
- Roshini Abraham, PhD
- Fred Lorey, PhD
SCID Collaborative Project

Welcome: Amy M Brower

True Positive Outliers

Analyte Type: Demographics
- TCR excision circle
- Control
- Confirmatory testing

Analyte: Selection
- BW (g)
- GA (wk)
- Cell age (days)
- Cell weight (g)

Analyte Type: Demographics
- TCR excision circle
- Control
- Confirmatory testing

Analyte: Selection
- RNaseP
- β-actin

Analyte Type: Demographics
- TCR excision circle
- Control
- Confirmatory testing

Analyte: Lymphocytes
- Hb
- Platelets
- WBC
- Neutrophils
- Monocytes
- Eosinophils
- CD45-flow
- CD3 T cells-flow
- CD4 T cells-flow
- CD8 T cells-flow
- CD19 B cells-flow
- NK cells-flow
- CD4 naïve T cells
- CD4 memory T cells
- CD8 naïve T cells

Newborn Screening Translational Research Network
86 Registered Users

- States Screening
- States Planning Screening
- International Groups
- NBSTRN
- NICHD
- APHL
- CDC
- Mayo

Screening States: 51%
Planning States: 28%
Other: 21%
<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Typical SCID</td>
<td>&lt;300 autologous T cells/u; Emergent Rx – HCT, enzyme or gene therapy</td>
</tr>
<tr>
<td>2</td>
<td>Leaky SCID/Omenn Syndrome</td>
<td>300-1500 autologous T cells at lower limit; Require HCT, enzyme or gene therapy</td>
</tr>
<tr>
<td>3</td>
<td>Variant SCID</td>
<td>Usually 300-1500 autologous T cells; May or may not require HCT</td>
</tr>
<tr>
<td>4</td>
<td>Syndromes with T Cell Impairment</td>
<td>&lt;1500 CD3 T cells/uL; Some require HCT or thymus Tx</td>
</tr>
<tr>
<td>5</td>
<td>Secondary T Cell Lymphopenia Excluding Preterm Infants Alone</td>
<td>&lt;=1500 CD3 T cells/uL; Includes conditions which cause non-intrinsic numerical T cell decrease</td>
</tr>
<tr>
<td>6</td>
<td>Preterm infants with T Cell Lymphopenia and No Other Recognizable Disorder</td>
<td>&lt;=1500 CD3 T cells/uL</td>
</tr>
</tbody>
</table>
77 Cases Classified

CA
NY
FL

Distribution of True Positive Cases

- Variant SCID: 20%
- IL2RG: 15%
- ADA: 7%
- IL7RA: 7%
- JAK3: 2%
- RAC2: 7%
- RAG1: 3%
- AK2: 3%
- CHARGE: 3%
- Trisomy 21: 2%
- Preterm alone: 2%
- Gastroschisis: 2%
- GI atresia: 2%
- Hypo left heart: 2%
- Third-spacing: 2%
- Congenital anomalies/NOS: 15%
- Other: 7%
- Undetermined: 2%

Newborn Screening Translational Research Network
NBSTRN Research Tools and Resources

**R4S**
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- Laboratory protocols, definitions

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**LPDR**
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**Stakeholder Engagement**
- Facilitate communication between experts and key stakeholders
- Monthly conference calls
Effort to Report on National Experience

- **Purpose** – To report on the efforts and findings of the state-based newborn screening programs and the clinicians who diagnose and treat newborns identified with SCID and related T lymphocyte deficiencies.

- **Scope** – This report describes the screening, diagnosis and treatment activities of states that are actively screening for SCID. This is a descriptive report only and will not include statistical analysis of the submitted data.
Next Steps

- Continued Training Key Stakeholders in Use of SCID Module
- Utilization of SCID Module by All States and Programs
- Publish SCID National Pilot Findings
- Describe National Experience with SCID Newborn Screening
- Continue Monthly Calls to Engage and Inform Stakeholders
NBSTRN is funded by a contract to the American College of Medical Genetics and Genomics from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (HHSN27520080001C)

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• Jennifer Puck, MD
• Robert Vogt, PhD
• Francis Lee, PhD
• Anne Marie Comeau, PhD

• Fred Lorey, PhD
• Mei Baker, MD
• Joanne Mei, PhD
• Carla Cuthbert, PhD

♦ Tonight International B 8:30pm – 9:15pm