Newborn Screening for SCID

Anne Marie Comeau, Ph.D
Deputy Director, NENSP
Professor of Pediatrics, UMMS
NEAN/Griffin Symposium
September 12, 2014
Disclosure

• Salary-Newborn Screening – NENSP-UMMS
Case 1

Term infant

DOL 3 NBS specimen received

Discharged home

DOL 7 seen for “weight check”
Case 1

Term infant

DOL 3 NBS specimen received

Discharged home/weekend

DOL 7 seen for “weight check”

DOL 8 Report Urgent Undetectable
Case 1

“weight check”

fam hx: 2/4 sibs died at 4 mos of pneumonia

Diagnosis: SCID CD3D
The Massachusetts SCID NBS Workgroup
Representatives from Newborn Screening, Immunology, Infectious Disease, Public Health and Transplantation

Baystate Children’s Hospital
BOSTON MEDICAL
Commonwealth of Massachusetts Department of Public Health
Children’s Hospital Boston
DANA-FARBER CANCER INSTITUTE
Floating Hospital for Children at Tufts Medical Center
MassGeneral Hospital for Children
UMass Memorial Medical Center

Dr. Anne Marie Comeau
Dr. Roger Eaton
Dr. Inderneel Sahai

Dr. Alicia Johnston
Dr. Ellen Rae Cooper
Dr. Alfred DeMaria
Dr. Tony Bonilla
Dr. Luigi Notarangelo
Dr. Sung-Yun Pai
Dr. Cody Meissner
Dr. Paul Hesterberg
Dr. Mark Pasternak
Dr. Jolan Walter
Dr. Beverly Hay
Dr. John Sullivan

New England Newborn Screening Program
2008

• Presentation to Massachusetts Newborn Screening Advisory Committee
• Refinement/feasibility of high throughput dried blood spot assay
• Proposal for CDC funding
SCID
Severe Combined Immunodeficiency

• “…a treatable inherited lack of cellular and humoral immunity…leading to death in early infancy unless immune reconstitution is provided.”

• Primary immunodeficiency
SCID
Severe Combined Immunodeficiency

• One of any of 13-20 different genetic conditions

• Common underlying characteristic: Complete absence or extremely low level of T cells
SCID
Severe Combined Immunodeficiency

- Bone Marrow Transplant
  Curative if successful
  50-95% success
  increased success if prior to infection

Alternative: early death
Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009

Sung-Yun Pai, M.D., Brent R. Logan, Ph.D., Linda M. Griffith, M.D., Ph.D., Rebecca H. Buckley, M.D., Roberta E. Parrott, B.S., Christopher C. Dvorak, M.D., Neena Kapoor, M.D., Imelda C. Hanson, M.D., Alexandra H. Filipovich, M.D., Soma Jyonouchi, M.D., Kathleen E. Sullivan, M.D., Ph.D., Trudy N. Small, M.D., Lauri Burroughs, M.D., Suzanne Skoda-Smith, M.D., Ann E. Haight, M.D., Audrey Grizzle, M.P.H., Michael A. Pulsipher, M.D., Ka Wah Chan, M.D., Ramsay L. Fuleihan, M.D., Elie Haddad, M.D., Ph.D., Brett Loechelt, M.D., Victor M. Aquino, M.D., Alfred Gillio, M.D., Jeffrey Davis, M.D., Alan Knutsen, M.D., Angela R. Smith, M.D., Theodore B. Moore, M.D., Marlis L. Schroeder, M.D., Frederick D. Goldman, M.D., James A. Connelly, M.D., Matthew H. Porteus, M.D., Ph.D., Qun Xiang, M.S., William T. Shearer, M.D., Ph.D., Thomas A. Fleisher, M.D., Donald B. Kohn, M.D., Jennifer M. Puck, M.D., Luigi D. Notarangelo, M.D., Morton J. Cowan, M.D., and Richard J. O'Reilly, M.D.
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D Age at Transplantation and Infection Status

- **Age ≤ 3.5 mo**
- **Age > 3.5 mo, infection resolved before transplantation**
- **Age > 3.5 mo, no infection before transplantation**
- **Age > 3.5 mo, active infection at transplantation**

Probability of Survival

Years

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CONCLUSIONS

Transplants from donors other than matched siblings were associated with excellent survival among infants with SCID identified before the onset of infection. All available graft sources are expected to lead to excellent survival among asymptomatic infants. (Funded by the National Institute of Allergy and Infectious Diseases and others.)
Massachusetts Pilot Testing Began February 1, 2009

Supported with grant funds for ~3 years

Grant # IV01-EH000362-03

Implementing SCID NBS with Multiplexed Assays in an Integrated Program Approach

CDC National Center for Environmental Health
Test Technology

TREC Analysis

Chan and Puck
J Allergy Clin Immunol
Feb 2005
High-Throughput Multiplexed T-Cell–Receptor Excision Circle Quantitative PCR Assay with Internal Controls for Detection of Severe Combined Immunodeficiency in Population-Based Newborn Screening


1 New England Newborn Screening Program, University of Massachusetts Medical School, Jamaica Plain, MA; 2 Division of Hematology-Oncology, Children’s Hospital Boston, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; 3 Wadsworth Center, New York State Department of Health, Albany, NY; 4 Department of Pediatrics, University of Massachusetts Medical School, Worcester, MA.
Massachusetts’ SCID NBS **Laboratory Testing** Algorithm

*(All TREC & RNaseP Values are copies/ul)*

Dried Blood Spot Specimen

*(Multiplex assay for TREC and RNaseP)*

- **TREC ≥ 503 and RNaseP ≥ 4032**
  - **SCREEN NEGATIVE** *(automated report)*
  - Two or Three tests with RNaseP < 4032
    - SCID-specific SCREEN UNSATISFACTORY
    - Phone call to PCP office to Request Repeat NBS specimen

- **RNaseP < 4032**
  - Prompts retest in duplicate of same specimen
  - Two or Three tests with RNaseP ≥ 4032
    - Two or Three tests with TREC ≥ 252
      - **SCREEN NEGATIVE** *(automated report)*
      - PHONE CONSULT with PCP and recommendation for repeat NBS and/or Flow Cytometry followed by fax of Screen Positive report packet

- **TREC < 503**
  - Prompted retest in duplicate of same specimen
  - Two or Three tests with RNaseP ≥ 4032
    - **SCREEN POSITIVE**
    - PHONE CONSULT with PCP and recommendation for repeat NBS and/or Flow Cytometry followed by fax of Screen Positive report packet
Guidelines for implementation of population-based newborn screening for severe combined immunodeficiency

Anne Marie Comeau • Jaime E. Hale • Sung-Yun Pai • Francisco A. Bonilla • Luigi D. Notarangelo • Mark S. Pasternack • H. Cody Meissner • Ellen Rae Cooper • Alfred DeMaria • Inderneel Sahai • Roger B. Eaton
SCID NBS Notification Algorithm Overview

SCREEN POSITIVE RESULT

REPEAT specimen TREC < cutoff

Was any previous specimen above cutoff?

yes → STOP
no → STOP

INITIAL TREC < cutoff

Request repeat NBS specimen

REPEAT SCREEN NEGATIVE

STOP

REPEAT TREC < cutoff or NOT DETECTABLE

Was any previous specimen above cutoff?

yes → PHONE CONSULT with PCP and recommendation for Flow Cytometry followed by fax of Screen Positive report packet
no → STOP

INITIAL TREC NOT DETECTABLE
Newborn Blood Spot Screening for Severe Combined Immunodeficiency by Measurement of T-cell Receptor Excision Circles; Approved Guideline
Data and Experience

401,156 infants screened for SCID

4 SCID

~1:100,000

Through 7/31/2014
401,156 infants screened for SCID (MA)

- 1,245 infants with positive SCID NBS result on *any* specimen

<table>
<thead>
<tr>
<th>SCID NBS</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Negative</td>
<td>99.7%</td>
</tr>
<tr>
<td>Positive</td>
<td>0.3%</td>
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</tbody>
</table>
401,156 infants screened for SCID (MA)

• 1,245 infants with positive SCID NBS result on any specimen
• 121 infants referred to Flow Cytometry* (~3/10,000)

4 SCID

~1:100,000

1 additional baby with leaky SCID (undergoing transplant)

1 additional baby with complete DiGeorge Syndrome
(referred for thymus transplant)

*by current algorithm
NICU vs. non-NICU status
in 1,245 infants with a positive SCID NBS on any NBS specimen

Nicu: n = 1,019
82%

Not Nicu: n = 227
18%
Final Screening Outcomes of 1,245 infants with any positive SCID NBS result
Final Screening Outcomes of 1,245 infants with any positive SCID NBS result

<table>
<thead>
<tr>
<th>Various Reported Clinical Statuses</th>
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<tbody>
<tr>
<td>• 71 cardiac defects</td>
</tr>
<tr>
<td>• 165 preemies</td>
</tr>
<tr>
<td>• 13 bowel issue/surgery or gastroschisis</td>
</tr>
<tr>
<td>• 3 diaphragmatic hernia</td>
</tr>
<tr>
<td>• 2 chylothorax</td>
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<tr>
<td>• 4 hypoxia/birth injury</td>
</tr>
<tr>
<td>• 4 liver failure</td>
</tr>
<tr>
<td>• 14 NEC</td>
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<tr>
<td>• 5 TEF</td>
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</tbody>
</table>

- 2 DiGeorge Syndrome
- 2 Jacobsen Syndrome
- 1 CHARGE
- 13 Trisomy 21
- 1 partial Trisomy 9
- 1 Miller-Dieker Syndrome (deletion on chromosome 17)
- 1 BARTH syndrome
- 3 with likely metabolic or mitochondrial disorders
- 1 Cystic Fibrosis (bowel obstruction)
- 1 Ehlers–Danlos syndrome
- 1 Toxoplasmosis

New England Newborn Screening Program
Final Screening Outcomes of 1,245 infants with any positive SCID NBS result

- Expired before Rpt NBS

- Various Reported Clinical Statuses
  - 6 reported cardiac defects
  - 1 chylothorax
  - 44 preemies

- All with explainable causes of death
  - 1 CHARGE likely
  - 2 Trisomy 21
  - 1 Trisomy 18
  - 1 Langerhans cell histiocytosis
  - 1 multiple congenital anomalies
Final Screening Outcomes of 1,245 infants with any positive SCID NBS result

- 5 likely DiGeorge Syndrome
- 1 VATER
- 3 likely Noonan Syndrome
- 1 Hirschsprung's disease
- 10 Trisomy 21
- 1 Trisomy 18
- 1 Sickle Cell Disease (FS)
- 1 Hirschsprung's disease
- 1 SCAD

Various Reported Clinical Statuses
- 25 bowel issue/surgery or gastroschisis
- 31 cardiac defects
- 2 chylothorax
- 1 cleft lip/palate
- 7 hypoxia/birth injury
- 12 withdrawl
- 15 NEC
- 2 TEF
- 2 multiple congenital anomalies
- 385 preemies

- 1 IPEX working dx (immune dysregulation disorder, immediately referred to immunology after +NBS due to clinical concern (rash))
- 1 DiGeorge Syndrome likely

Various Reported Clinical Statuses
- 2 dysmorphic
- 9 with jaundice
- 5 slow weight gain
- 100 noted as “well”
Final Screening Outcomes of 1,245 infants with any positive SCID NBS result

- Prev NBS: 300
- Expired before Rpt NBS: 0
- Rpt NBS: 500
- Prompted Flow: 0

- NICU:
  - Prev NBS: 300
  - Rpt NBS: 500

- Not NICU:
  - Expired before Rpt NBS: 0
  - Prompted Flow: 0
Status of 121 Infants Prompting Flow Cytometry

- **Idiopathic t cell lymphopenia** n= 24
- **Preterm** n= 7
- **Secondary t cell lymphopenia** n= 16
- **Other Syndrome** n= 8
- **DiGeorge Syndrome* n= 23** *Includes 1 Complete DiGeorge needing thymus transplant
- **SCID n= 4**
- **Flow WNL n= 13**
- **Expired before flow** n= 5
- **Resolved with Rpt NBS** n= 4
- **OOC/OOS n= 2**
- **Closed n= 24**
- **Pending n= 10**
- **Other n= 3**

+1 Pending flow
+1 Leaky SCID
TREC Results of Infants to Flow

Prompting flow (either undetectable or 2 OOR TREC)
n = 121
~1 in 30 risk for SCID

<table>
<thead>
<tr>
<th>Undetectable TREC</th>
<th>SCID</th>
<th>Not SCID</th>
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</thead>
<tbody>
<tr>
<td>NICU</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Not NICU</td>
<td>2</td>
<td>5*</td>
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</table>

<table>
<thead>
<tr>
<th>Never Normal TREC</th>
<th>SCID</th>
<th>Not SCID</th>
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</thead>
<tbody>
<tr>
<td>NICU</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>Not NICU</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
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TREC Results of Infants to Flow

Prompting flow
(either undetectable or 2 OOR TREC)

- n = 121
- ~1 in 30 risk for SCID

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<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Not NICU</td>
<td>2</td>
<td>5*</td>
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</table>

~1 in 9

<table>
<thead>
<tr>
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<th>Not SCID</th>
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<tr>
<td>NICU</td>
<td>1</td>
<td>72</td>
</tr>
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<td>0</td>
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**TREC Results of Infants to Flow**

Prompting flow
(either undetectable or 2 OOR TREC)
n= 121
~1 in 30 risk for SCID

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<td>5*</td>
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~1 in 9

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<th>Not SCID</th>
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<td>1</td>
<td>72</td>
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<tr>
<td>Not NICU</td>
<td>0</td>
<td>22</td>
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</table>

~1 in 15
Positive Predictive Values of SCID NBS

121 infants referred to Flow Cytometry*

PPV for SCID: 4/121 3%
PPV for TCL: 96/109 88%

*by current algorithm
## Treatment of Infants Identified with SCID by NBS in MA

<table>
<thead>
<tr>
<th>ID</th>
<th>SCID Type</th>
<th>Treatment (ERT, GT, or Donor Type)</th>
<th>Age at HCT (mo)</th>
<th>Conditioning Regimen</th>
<th>Time since HCT (mo)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>JAK3</td>
<td>9/10 HLA-A mismatched unrelated</td>
<td>2.5</td>
<td>Busulfan, cyclophosphamide, ATG</td>
<td>49</td>
<td>Alive, at home, off IVIG, vaccinated, no GVHD</td>
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<tr>
<td>2</td>
<td>TTC7A (SCID+MIA)</td>
<td>sibling 9-10/10</td>
<td>3</td>
<td>ATG x 3d</td>
<td>37</td>
<td>Alive, at home, off IVIG, vaccinated, no GVHD</td>
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<tr>
<td>3</td>
<td>IL2RG</td>
<td>10/10 unrelated</td>
<td>2.5</td>
<td>Busulfan, fludarabine, ATG</td>
<td>36</td>
<td>Alive, at home, off IVIG, vaccinated, vitiligo, no GVHD</td>
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<tr>
<td>4</td>
<td>CD3D</td>
<td>10/10 unrelated</td>
<td>2.5</td>
<td>Busulfan, fludarabine, ATG</td>
<td>34</td>
<td>Alive, at home, off IVIG, no GVHD</td>
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</tbody>
</table>

### Notes
- ERT: Enzyme Replacement Therapy
- GT: Gene Therapy
- Donor Type: HLA-A mismatched unrelated
- Conditioning Regimen: Busulfan, cyclophosphamide, ATG
- Time since HCT: 49 months
- Outcomes: Alive, at home, off IVIG, vaccinated, no GVHD
NICU contacts (babies)

by NICU that took report of initial OOR result
# NICU contacts

<table>
<thead>
<tr>
<th></th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8a</th>
<th>#8b</th>
<th>#8c</th>
<th>#9</th>
<th>#10</th>
<th>SCNs</th>
<th>PCP</th>
<th>OOS</th>
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<tbody>
<tr>
<td>TOTAL Babies</td>
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<tr>
<td>(specimens)</td>
<td>112</td>
<td>88</td>
<td>78</td>
<td>42</td>
<td>98</td>
<td>56</td>
<td>69</td>
<td>143</td>
<td>118</td>
<td>19</td>
<td>25</td>
<td>29</td>
<td>38</td>
<td>55</td>
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<tr>
<td># BABY contacts per</td>
<td>20</td>
<td>16</td>
<td>14</td>
<td>7</td>
<td>18</td>
<td>10</td>
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<td># REPORTS per year</td>
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<td>23</td>
<td>18</td>
<td>10</td>
<td>24</td>
<td>14</td>
<td>21</td>
<td>50</td>
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<td># that had flow</td>
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<td>1</td>
<td>2</td>
<td>4</td>
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<td>7</td>
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<td>before algo change</td>
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<tr>
<td>Typical # BABIES</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
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<td>0.5</td>
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<tr>
<td>needing flow per</td>
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New England Newborn Screening Program
TRECs and Gestational Age

Review of ~10,000 TREC results linked to GA

<table>
<thead>
<tr>
<th></th>
<th>TRECs (copies/ul)</th>
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<tbody>
<tr>
<td>Overall Median</td>
<td>1,368</td>
</tr>
<tr>
<td>Gest Age &lt;37 weeks</td>
<td>1,060</td>
</tr>
<tr>
<td>Gest Age &gt;=37 weeks</td>
<td>1,397</td>
</tr>
</tbody>
</table>

98% of babies with a gestational age <37 weeks had WNL TREC results

99.9% of babies with a gestational age >=37 weeks had WNL TREC results
TRECs and Gestational Age

Review of ~10,000 TREC results linked to GA

Cleaned (initial specimens obtained by <=7 days of age)
Case 2

Term infant

Extremely sick infant; abdominal surgeries; metabolics a bit off

Clinical focus CF, CF screen negative

SCID positive -
Case 2

Infant reportedly DNR

Multiple caregivers

SCID NBS was new, SCID is rare

SCID can look like CF
Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States

Antonia Kwan, PhD, MRCPCH; Roshini S. Abraham, PhD; Robert Currier, PhD; Amy Brower, PhD; Karen Andruszewski, BS; Jordan K. Abbott, MD; Mei Baker, MD; Mark Ballow, MD; Louis E. Bartoshesky, M★ Francisco A. Bonilla, MD, PhD; Charles Brokopp, DrPH; Edward Brooks, MD; Michele Caggana, ScD; Jocelyn Celestin, MD; Joseph A. Church, M★ Anne Marie Comeau, PhD; James A. Connelly, MD; Morton J. Cowan, MD; Charlotte Cunningham-Rundles, MD; Trivikram Dasu, PhD; Nina Dave, MD; Maria T. De La Morena, MD; Ulrich Duffner, MD; Chin-To Fong, MD; Lisa Forbes, MD; Debra Freedenberg, MD; Erwin W. Gelfand, M★ Jaime E. Hale, BS; I. Celine Hanson, M★ Beverly N. Hay, MD; Diana Hu, MD; Anthony Infante, MD, PhD; Daisy Johnson, BSN; Neena Kapoor, MD; Denise M. Kay, PhD; Donald B. Kohn, MD; Rachel Lee, PhD; Heather Lehman, MD; Zhilli Lin, PhD; Fred Lorey, PhD; Aly Abdel-Mageed, MD, MBA; Adrienne Manning, BS; Sean McGhee, MD; Theodore B. Moore, MD; Stanley J. Naides, MD; Luigi D. Notarangelo, MD; Jordan S. Orange, M★ Sung-Yun Pai, MD; Matthew Porteus, MD, PhD; Ray Rodriguez, MD, JD, MPH, MBA; Neil Romberg, MD; John Routes, MD; Mary Ruehle, MS; Arve Rubenstein, MD; Carlos A. Saavedra-Matiz, MD; Ginger Scott, RN; Patricia M. Scott, MT; Elizabeth Secord, MD; Christine Seroogy, MD; William T. Shearer, MD, PhD; Subhadra Siegel, MD; Stacy K. Silvers, MD; E. Richard Stiehm, MD; Robert W. Sugerman, MD; John L. Sullivan, MD; Susan Tankesley, PhD; Millard L. Tierce IV, DO; James Verbsky, MD, PhD; Beth Vogel, MS; Rosalyn Walker, MD; Kelly Walkovich, MD; Tolan E. Walter, MD, PhD; Richard L. Wasserman, MD, PhD; Michael S. Watson, MS, PhD; Geoffrey A. Weinberg, MD; Leonard B. Weiner, MD; Heather Wood, MS; Anne B. Yates, MD; Jennifer M. Puck, MD

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<tr>
<th>Table 1. Classification of Conditions With Low T-Cell Receptor Excision Circles and Low T-Cell Numbers Found by Newborn Screening</th>
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<tbody>
<tr>
<td><strong>Definition of Condition</strong></td>
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<tr>
<td><strong>CD3 T Cells/μL</strong></td>
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<tr>
<td>Primary Targets of Newborn Screening</td>
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<tr>
<td>Typical SCID⁵</td>
</tr>
<tr>
<td>Leaky SCID⁵</td>
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<tr>
<td>Omenn syndrome</td>
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<tr>
<td>Secondary Targets of Newborn Screening</td>
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<tr>
<td>Syndrome with low T-cell numbers</td>
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<tr>
<td>Secondary T-cell lymphopenia</td>
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<tr>
<td>Preterm birth alone</td>
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<tr>
<td>Idiopathic T-cell lymphopenia, also called variant SCID</td>
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<td>Duration of screening included, mo</td>
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<tr>
<td>Infants screened, No. (^a)</td>
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<tr>
<td>Flow cytometry referrals, (^b) No. (%) ([95% CI]^{c})</td>
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<tr>
<td>SCID cases</td>
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<tr>
<td>SCID incidence</td>
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<tr>
<td>SCID cases per 100000 screened, No. ([95% CI]^{c})</td>
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<td>SCID infant survival, No./Total No. (%) ([95% CI]^{c,e})</td>
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</tbody>
</table>
The future?

Other immunodeficiencies?

Other conditions multiplexed to this technology?

Both?

Thank you.