Newborn Screening for SCID and…?

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Implementing SCID NBS with Multiplexed Assays in an Integrated Program Approach
CDC National Center for Environmental Health

Patient Recruitment and Consent
UMMS Life Sciences Moment Fund Grant # UL1TR000161
National Center for Advancing Translational Sciences

A Retrospective Study with Prospective Potential: evaluating specimens of children diagnosed with conditions that may be identifiable in the newborn period by molecular testing for measures of T and B cell development

New England Newborn Screening Program
The Massachusetts SCID NBS Workgroup

Representatives from Newborn Screening, Immunology, Infectious Disease, Public Health and Transplantation

Baystate Children’s Hospital
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

Children’s Hospital Boston

Dana-Farber Cancer Institute

Floating Hospital for Children at Tufts Medical Center

Mass General Hospital for Children

UMass Memorial Medical Center

New England Newborn Screening Program
Status of 121 Infants Prompting Flow Cytometry

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

New England Newborn Screening Program

University of Massachusetts Medical School
<table>
<thead>
<tr>
<th>Condition</th>
<th>CD3 T Cells/μL</th>
<th>Proliferation to PHA</th>
<th>Other Supporting Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Targets of Newborn Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical SCID&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;300 (autologous)</td>
<td>&lt;10% of normal</td>
<td>Detectable maternal T cells in peripheral blood; proven deleterious defect(s) in a known SCID gene</td>
</tr>
<tr>
<td>Leaky SCID&lt;sup&gt;a&lt;/sup&gt;</td>
<td>300-1500, few naive T cells</td>
<td>Reduced (10%-50% of normal)</td>
<td>No maternal T cells detectable; incomplete defect(s) in a known SCID gene</td>
</tr>
<tr>
<td>Omenn syndrome</td>
<td>Oligoclonal T cells</td>
<td>Reduced (10%-50% of normal)</td>
<td>Erythroderma, hepatosplenomegaly, eosinophilia, and elevated levels of serum IgE antibody</td>
</tr>
<tr>
<td><strong>Secondary Targets of Newborn Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syndrome with low T-cell numbers</td>
<td>Recognized genetic syndrome that includes low T-cell numbers within its spectrum of clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary T-cell lymphopenia</td>
<td>Congenital malformation or disease process without an intrinsic defect in production of circulating T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth alone</td>
<td>Preterm birth and low birth weight, with low T-cell numbers early in life that normalize over time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic T-cell lymphopenia, also called variant SCID</td>
<td>Low T-cell numbers without recognized cause; 6 programs used 300-1500 autologous T cells/μL plus evidence of functional immune cell impairment, while other programs included infants with higher T-cell numbers (see Table 4).&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Diagnoses of 411 Infants With Non-SCID T-Cell Lymphopenia Identified by Newborn Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified T-cell lymphopenia$^f$</td>
<td>117</td>
</tr>
</tbody>
</table>

*JAMA. 2014;312(7):729-738. doi:10.1001/jama.2014.9132*
To what extent is neonatal T-cell lymphopenia an early indicator of later diagnoses?

• Monitor infants identified with idiopathic T-cell lymphopenia
  Long term – multi– year prospective follow up

• Retrieve and test NBS specimens of older children who carry specific diagnoses
To what extent would a TREC/KREC assay help to define later diagnoses associated with neonatal T-cell lymphopenia?

• Evaluate T and B cell profiles of older children with specific diagnoses Representative of neonatal profile?

• Retrieve and test NBS specimens of older children who carry specific diagnoses
Retrieve and test NBS specimens of older children who carry specific diagnoses

Retrospective Study with Prospective Potential
Retrieve and test NBS specimens of older children who carry specific diagnoses

- assays for TREC and KREC
- multiplex TREC/KREC/RNaseP
- Patient cohort
  Patients with defined diagnoses and likely T or B cell dysfunction
van Zelm MC, van der Burg M, Langerak AW, van Dongen JJ. PID comes full circle: applications of V(D)J recombination excision circles in research, diagnostics and newborn screening of primary immunodeficiency disorders. Front Immunol 2011;2:12


# VALIDATION OF MULTIPLEX ASSAY WITH RESIDUAL SAMPLES FROM SCID PATIENTS

<table>
<thead>
<tr>
<th>SCID TYPE</th>
<th>PHENOTYPE</th>
<th>TREC</th>
<th>KREC</th>
<th>RNaseP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL7RA</td>
<td>T-B+NK+</td>
<td>0</td>
<td>387</td>
<td>37761</td>
</tr>
<tr>
<td>ADA</td>
<td>T-B-NK-</td>
<td>0</td>
<td>0</td>
<td>9006</td>
</tr>
<tr>
<td>IL2RG</td>
<td>T-B+NK-</td>
<td>0</td>
<td>542</td>
<td>32071</td>
</tr>
<tr>
<td>PNP</td>
<td>progressive loss T</td>
<td>0</td>
<td>6</td>
<td>33316</td>
</tr>
<tr>
<td>ADA</td>
<td>T-B-NK-</td>
<td>0</td>
<td>0</td>
<td>58987</td>
</tr>
<tr>
<td>IL2RG+MAT engraft</td>
<td>T-B+NK-</td>
<td>0</td>
<td>742</td>
<td>59968</td>
</tr>
<tr>
<td>CD3D</td>
<td>T-B+NK+</td>
<td>0</td>
<td>219</td>
<td>33413</td>
</tr>
</tbody>
</table>
Median TREC and KREC values by Condition
All Available Patient Specimens

- Median TREC and KREC values are presented for various conditions, including CMV, CVID, DiGe, SCID MIA, TRI 21, W A, and XLA.
- The graph compares PT TREC, CTR TREC, pt KREC, and ctr KREC across these conditions.
- The x-axis represents different conditions, while the y-axis shows the median values ranging from 0 to 2000.

Commonwealth Medicine
Median TREC and KREC values by Condition
All Available Patient Specimens
TREC and KREC profiles in neonatal specimen of each infant

TREC and KREC profiles associated with various conditions:
- ALL
- ALL TRISOMY 21
- ATAX TEL
- CMV
- CVID
- DiGeorge
- SCID MIA
- TRI 21
- Wiskott Aldrich
TREC and KREC profiles in neonatal specimen of each infant

- TREC and KREC profiles associated with various conditions
- ALL
- ALL TRISOMY 21
- ATAX TEL
- CMV
- CVID
- DiGeorge
- SCID MIA
- TRI 21
- Wiskott Aldrich

Graph showing the distribution of TREC and KREC profiles in neonatal specimens.
TREC and KREC profiles in neonatal specimen of each infant

- ALL
- ALL TRISOMY 21
- ATAX TEL
- CMV
- CVID
- DiGeorge
- SCID MIA
- TRI 21
- Wiskott Aldrich
Conclusions

- KREC in first tier is necessary to identify XLA
- Other non-SCID PID show early profile T-B- PID
- Multiplex TREC KREC shows early profile indicative of B- SCID
- Population data needed