Establishing Follow-up Protocols for Low Frequency Events in SCID NBS: working with Specialists New to Newborn Screening

2011 Newborn Screening and Genetics Testing Symposium
San Diego, CA

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Current Work-up Algorithm

**Flow Cytometry:**
CD3, CD4, CD8, CD16/56, CD19
naïve T cell determination

**Clinic Referral if:**
total T cell number <2500
naïve % <50%
any other abnormality

**Clinic Referral inclusive of:**
Functional testing
Physical Exam

**Genotyping/Karyotyping if:**
Suspected SCID
Suspected DiGeorge, other

**Referral to Transplant Center for:**
SCID
202,298 infants screened for SCID

• 644 infants with positive SCID NBS result on any specimen
202,298 infants screened for SCID

- 644 infants with positive SCID NBS result on any specimen

SCID NBS
Negative 99.7%

SCID NBS
Positive 0.3%
202,298 infants screened for SCID

• 644 infants with positive SCID NBS result on any specimen
• 44 infants referred to Flow Cytometry*

*by current algorithm
Quality Improvements to Referral and Work-up Algorithms

<table>
<thead>
<tr>
<th>First</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC &lt;252, refer for flow</td>
<td>Undetectable TREC on initial specimen → immediate flow</td>
</tr>
<tr>
<td></td>
<td>TREC &lt;252 on initial → request repeat DBS</td>
</tr>
<tr>
<td></td>
<td>Serial TREC &lt;252 and no interim in-range TREC → flow</td>
</tr>
<tr>
<td></td>
<td>Any in-range TREC on a specimen from same infant → no flow</td>
</tr>
<tr>
<td>Flow at any of 4 qualified centers</td>
<td>Flow at any of 4 qualified centers</td>
</tr>
<tr>
<td>Specifications for use of gold standard pediatric functional testing</td>
<td></td>
</tr>
</tbody>
</table>
NICU vs. non-NICU status in 644 infants with a positive SCID NBS on any NBS specimen

- NICU: n = 502, 78%
- Non-NICU: n = 142, 22%
Outcomes of 644 infants with any positive SCID NBS result

- Prev WNL: NICU: X, not NICU: X
- Rpt WNL: NICU: 350, not NICU: 100
- Expired before Rpt: NICU: 50, not NICU: 10
- Flow: NICU: 50, not NICU: 10

Legend: NICU, not NICU
## US PILOT STUDIES
### INTERIM FINDINGS
Combined data from CDC and NICHD-funded pilots (through April 2011)

<table>
<thead>
<tr>
<th>State</th>
<th>WI</th>
<th>MA</th>
<th>NY</th>
<th>CA</th>
<th>PR</th>
<th>LA</th>
<th>TOT</th>
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</thead>
<tbody>
<tr>
<td>screened</td>
<td>243,707</td>
<td>161,707</td>
<td>136,635</td>
<td>358,000</td>
<td>29,000</td>
<td>31,464</td>
<td>960,513</td>
</tr>
<tr>
<td>SCID</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>rate (1/x)</td>
<td>61,000</td>
<td>161,707</td>
<td>34,000</td>
<td>72,000</td>
<td></td>
<td></td>
<td>69,000</td>
</tr>
</tbody>
</table>

Increased incidence **extent?**

48% ➔ 10% X-linked?

6% ➔ 65% Hispanic?
SCID NBS Diagnoses

MA SCID NBS Working group conference
Sampling...when even a million might not be enough to give all the answers

| Cystic fibrosis | 1/3,000 | 30 | SCID | 1/100,000 |
Sampling...when even a million might not be enough to give all the answers

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<th>Cystic fibrosis</th>
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<td>1/3,000</td>
<td></td>
<td>1/100,000</td>
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<tr>
<td>30 months timeline</td>
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Sampling...when even a million might not be enough to give all the answers

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30 days timeline

30 months timeline
Sampling...when even a million might not be enough to give all the answers

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30 days timeline

30 months timeline

MERGE TIMELINES?

30 days
30 months
NBS Diagnoses
<table>
<thead>
<tr>
<th>Lymphocyte Profile</th>
<th>SCID type</th>
<th>Donor/Regimen</th>
<th>Status</th>
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<tbody>
<tr>
<td>T- B+ NK-</td>
<td>JAK3</td>
<td>9/10 mismatched unrelated Busulfan, cyclophosphamide ATG</td>
<td>Transplanted At home, well</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T- B+ NK+</td>
<td>MIA; sub-type unknown 9/10 rej; 10/10 GVHD sibling ATG</td>
<td>Transplanted, at home, engrafting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL2RG</td>
<td>10/10 unrelated Busulfan, fludarabine, ATG</td>
<td>Transplanted</td>
</tr>
<tr>
<td>T- B+ NK-</td>
<td>CD3D</td>
<td>pending</td>
<td>Awaiting transplant</td>
</tr>
<tr>
<td>T- B+ NK+</td>
<td></td>
<td></td>
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Pearls from...experience

• Continuous quality measures
  – For the screening laboratory
  – For the diagnostic workup
  – For what we can do about communications

• Projections...are only projections...
Status of 44 Infants with Out Of Range SCID NBS Prompting Flow Cytometry

- Closed to Further Follow-up: n = 18
- SCID: n = 4
- DiGeorge and Clinical DiGeorge: n = 7
- Other “Condition”: n = 2
- Flow Pending: n = 2
- Not SCID – T cell lymphopenia: n = 11
- Expired: n = 4
- Flow WNL: n = 4
- Cleared by Immunology: n = 7
- Resolved With Repeat NBS: n = 2
- Out of Country: n = 1