Newborn Screening for SCID in a High Risk population

Why Arizona should include TREC screening in the routine newborn screen
Silly Wabbit, TRECs are for SCIDS!

(Apologies to General Mills and the fans of TRIX cereal...)
Premise

- TREC screening for SCID and other T cell deficiencies is a low cost, highly specific and sensitive test that is easily incorporated into a NB screening protocol.

- Arizona is home to 6 NA tribes with disproportionately high rates of SCID that would benefit greatly from universal screening protocols.

- Early detection and treatment of SCID and other T cell deficiencies can have great impact on the lives of affected children.
A case history

- 2mo old F infant presents with resp distress and shock
- Baby born as term healthy Navajo female infant to a 19yo G1 mom from Page, AZ.
- Home with mom at 48 hours of age
A case history

- Resuscitation in Page ED with intubation, mechanical ventilation, vasopressors, blood transfusion.
- Pulm hemorrhage as well as pneumonitis on CXR
  - No thymus on CXR
- Transferred to Cardon Children’s Hospital. S Pneumoniae sepsis.
A case history

- Improvement in sepsis with antibiotics and supportive care

- However, baby with encephalopathic neuro exam. CMV PCR(+) in CSF
  - From breast feeding?
  - From transfusions?

- Transferred to UCSF at 3 weeks into hospitalization for stem cell transplantation
A case history

- Peripheral stem cell transplant, haplotype matched donor
- Now 3 yo, T cell engrafted
  - Routine IVIG monthly
- Severe neurologic damage
A happier case

- Term healthy Navajo baby born to a 23 yo G3 mom at Tuba City
- Presents at 6 week of age with croup and fever
  - Feb 2009- RSV season...
    - but RSV and Flu rapid tests(-)
  - Has a prolonged course- still has stridor at 48 hrs
  - Ulceration noted perianal area
  - No thymus on CXR
A happier case

- WBC- 8.1K, ALC 1500
- Transferred to PCH for evaluation, R/o SCID
- SCID-A diagnosis made
- Stem cell transplant within 2 weeks
  - HLA matched sibling donor
- Full engraftment at 6mos
  - Normal development
WHO Criteria Screening

- Condition an important health problem
- Cost of case finding reasonable
- Recognizable in latent phase
- Effective treatment available
- Acceptable to population tested
SCID meets these criteria

- **A lethal disorder** not detectable at birth by routine examination
  - Death comes from overwhelming infection in infancy

- **Incidence of disease is significant** in the US but especially in AZ

- **TREC testing now available** to screen patients
  - Cost per test as low as $6 per test commercially

- **Confirmatory testing available**
  - Flow cytometry

- **Treatment available**- potentially curative
  - Stem cell transplant
  - Gene therapy
SCID

- Lack of cellular immunity  T-, B- SCID
  - Missing T lymphocytes – responsible for defense against viral and fungal infection, facilitate antibody production and recognition of foreign proteins and germs, immune memory cells
  - Missing B lymphocytes - make antibodies (immunoglobulins) responsible for processing germs for destruction by other elements of the immune system, give immune memory against many infections
  - Bacterial, viral, fungal infections can all become lethal, even with antimicrobial treatment
Natural history of SCID

- Usually are born looking normal
- Mouth Ulcers/perianal ulcers
- Recurrent thrush
  - Fungal infection of the mouth
- Failure to gain weight
  - Recurrent diarrhea
- Skin rash
- Inability to fight off infection acquired in 1st year of life
- Usually fatal in by age 2 if not treated
SCID--Diagnosis before NB screening

- how to make early diagnosis possible?
- Screening tests- CXR, CBC with ALC
- If concerned
  - lymphocyte subsets and function tests
    - Requires live cells
    - Requires 8 ml blood
    - Requires Fed Ex to reference lab
    - potential delay of 1-2 weeks to get results back
    - cost ~$800
SCID dx

- Problem: when to be concerned?
- If no family history, SOMETHING BAD HAS TO HAPPEN TO TRIGGER THE DX EVALUATION.
  - That something bad could be a fatal event or one that leaves long lasting consequences
  - avg. age at diagnosis usually 4-6 mos.
Treatment of SCID

- Give them a new immune system
  - Bone marrow transplant
  - Peripheral stem cell transplant
  - Umbilical cord blood transplant
- All are a source of the stem cells that eventually will mature into lymphocytes
- Donor - usually a sibling or parent
  - BMT services available in AZ and CA
Why is this specifically important for AZ?

- Athabascan tribes have a specific gene mutation on the Artemis gene (10p) that is associated with SCID
- Carrier frequency estimated at 1:30 on the Western Navajo reservation
- Incidence of SCID 1:2000 births Western Navajo
  - As frequent as many of the other conditions we screen for— and is potentially CURABLE with early intervention
SCID-A

- Athabascan type SCID- T-B- NK+
- Higher incidence in Athabascans: Dene, Navajos, and Apaches than any other ethnic group
  - 1st described in 1982- descriptive paper on 4 children seen at Denver
- General population incidence 1:100,000
  - Western Navajo population incidence 1:2000
SCID-A

- 46 Athabascan children in the Southwest since 1978
  - 31 Navajo children
  - 3 Athabascan (Dene) children from NW Canada

- Cases found in San Carlos, Whiteriver, Mescalero (NM), Jicarilla (NM) Apache tribal members and Ramah Navajo
SCID-A outcome

- Success of therapy directly correlated with early identification of patients and transplant < 2mos of age

- Many children with SCID have had delay in diagnosis leading to permanent morbidity or death
## Pilot projects results -

<table>
<thead>
<tr>
<th>Pilot</th>
<th>Annual Births/Pilot Target</th>
<th>Date: Start of Screening</th>
<th>Months Screening</th>
<th>Number of Infants Screened as of March 31, 2011</th>
<th>SCID</th>
<th>SCID Variant</th>
<th>Non SCID</th>
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<tbody>
<tr>
<td>Wisconsin</td>
<td>69,232</td>
<td>1/1/2008</td>
<td>39</td>
<td>225,004</td>
<td>4</td>
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<td>7</td>
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<td>Massachusetts</td>
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<td>2/1/2009</td>
<td>26</td>
<td>161,707</td>
<td>1</td>
<td>0</td>
<td>14</td>
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<tr>
<td>Navajo Nation</td>
<td>2,000</td>
<td>2/1/2009</td>
<td>26</td>
<td>1,297</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>California</td>
<td>510,000</td>
<td>8/1/2010</td>
<td>8</td>
<td>340,000</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Puerto Rico</td>
<td>45,620</td>
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<td>29,115</td>
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<td>0</td>
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<tr>
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<td>118,328</td>
<td>2</td>
<td>2</td>
<td>9</td>
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<tr>
<td>Louisiana</td>
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<td>10/1/2010</td>
<td>6</td>
<td>32,634</td>
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<td>0</td>
<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>119</strong></td>
<td></td>
<td><strong>914,557</strong></td>
<td></td>
<td><strong>12</strong></td>
<td><strong>7</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

Data as of May 2011

Courtesy: Amy Brower & SACHDNC
Navajo Nation pilot

- CDC Grant received to start screening
- 2 year project- screened ~2000 babies at Chinle and Tuba City
  - 60% participation
  - Test was acceptable to population
    - Most refusals were because of belief that baby was healthy and did not need testing
    - 3 false positives found, normal on recheck
- One infant with T cell deficiency and DiGeorge variant found by screening
Navajo Nation screening

- Donation of 6000 tests from Perkin Elmer genetics
- Implemented universal screening Feb 2012 at 6 delivering hospitals on NN
  - 1 still pending.
- 550 children screened as of May 31, 2012
- But what about those babies who are not born on the reservation?
## Incidence calculations

<table>
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<tr>
<th>Diagnosis</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>SCID</td>
<td>1 in 68,000</td>
</tr>
<tr>
<td>SCID Variant</td>
<td>1 in 68,000</td>
</tr>
<tr>
<td>SCID + SCID Variant</td>
<td>1 in 34,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State*</th>
<th>CA</th>
<th>NY</th>
<th>MA</th>
<th>WI</th>
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<tbody>
<tr>
<td>SCID</td>
<td>1 in 68,000</td>
<td>1 in 59,164</td>
<td>1 in 161,707</td>
<td>1 in 56,251**</td>
</tr>
<tr>
<td>SCID Variant</td>
<td>1 in 68,000</td>
<td>1 in 59,164</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SCID + SCID Variant</td>
<td>1 in 34,000</td>
<td>1 in 29,582</td>
<td>1 in 161,707</td>
<td>1 in 56,251**</td>
</tr>
</tbody>
</table>

*Incidence is generally higher than previously reported*
HHS recommendation

- Jan 2010- Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC) recommends to HHS to add for inclusion to mandatory NB screening panel
  - May 2010 Sibelius formal announcement

- 2011- 10 states/terr have adopted
  - Wisc, Mich, Mass, Calif, Conn, Colorado, Del, Louisiana, New York, Puerto Rico
  - Navajo Nation, Penn, Texas pilot programs
  - Vetoed Fla
  - Texas just approved May 2012 after previous veto!
    (800,000 tests per year!)
Arizona

- 2010 census
  - 4.6% AIAN population
  - 5.5% with more than one race listed
  - 21 federally recognized tribes
    - 6 Athabascan tribes
AZ births

- ADHS stats 2010
  - Births- 6.8% of AZ births with AI/AN mother (5815 births)
  - Over 87,000 births per year
- Likely to find 2 to 3 cases SCID per year
  - Likely to find more cases of other t cell deficiencies annually
Summary

- TREC screening for SCID and other T cell deficiencies is a low cost, highly specific and sensitive test that is easily incorporated into a NB screening protocol.

- Arizona is home to 6 NA tribes with disproportionately high rates of SCID that would benefit greatly from universal screening protocols.

- Early detection and treatment of SCID and other T cell deficiencies can SAVE LIVES and $$
QUESTIONS?

- Diana.hu@tchealth.org
Inheritance of SCID

- Autosomal recessive
  - Mom and dad are asymptomatic carriers
  - 1:4 chance of infant being affected
  - 1:2 chance of other children as carriers
- Specific unique gene mutation found in Athabascan population
Gene Mutation for SCID-A

- In a gene called *Artemis* located on Chromosome 10
  - Responsible for development of diversity of immunoglobulins and T-cell receptors in the immune system
  - May have effects on the ability of DNA to repair after damage

- Estimated carrier freq 1:30 western reservation Navajo
Why is it higher in Athabascans?

- Founder effect - a gene rare in the general population occurs in a small, isolated, rapidly expanding population which leads to an increased gene frequency and increased frequency of disease in that population.
After population reduction: gene frequency - 1:10

Initial gene frequency - 2:100
SCID-A –Navajo experience

- 31 Navajo children since 1978
  - 23 since 1987
- 1/8 long term survivors born between 1978-1987
  - Survivor diagnosed clinically at age 6 weeks with NOMA, transplanted age 3 months
  - Only 4/8 transplanted- others too ill at the time of diagnosis for transplant
SCID-A—Navajo experience

- Since 1987
  - 16/23 long term survivors
    - 22 transplanted UCSF, Duke, Sloan Kettering, Denver, PCH
    - 1 not transplanted due to severe infection at time of diagnosis
  - 5/6 children who died after transplant were identified after age 4 months
    - Presented with recurrent or persistent infection
    - 1/6 who was identified at birth died age 21 chronic lung disease
SCID in Athabascans

- Also have had 2 families with other forms of SCID (not SCID-A)
  - 2 brothers with X linked
  - 1 female with T-B+ SCID

- *success of therapy correlated with age at transplant (< 2 months of age)*
T cells

- Have specific binding receptors that are unique to a specific antigen that they will attack.
TRECs

- T cell receptor excision circle (TREC)
- Extra DNA that is snipped out when making the DNA sequence that codes for a unique receptor
  - Part of normal T cell maturation
  - Numbers of TRECs are a reflection of the population of recently formed T cells in the blood
- Cost ~$6 per test
Newborn screening test

- Uses a tiny amount of blood
  - About 9 microliters from two punches
- DNA is extracted from the blood sample
- TREC numbers are counted
  - < 30 copies is associated with very low T-cell numbers
    - Would be clinically verified with standard T-cell subsets and function tests. (flow cytometry)
Newborn screening technology