Newborn Screening for Severe Combined Immune Deficiency (SCID)

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Disclosures

• None
Warning Signs of Immunodeficiency

www.info4Pl.org

• 4 or more new episodes of otitis in 1 year
• 2 or more serious sinus infections in 1 year
• 2 or more months on antibiotics without resolution
• 2 or more radiographically proven pneumonia in 1 year
• Failure to grow (weight and/or height)
• Recurrent deep skin or organ abscesses
• Persistent thrush of mouth, nails, skin
• IV antibiotics required for infection clearance
• 2 or more deep-seated infections including bacteremia
• Family history of PIDD
Primary Immunodeficiency Disorders

- Antibody 50%
- Combined 20%
- Phagocytic 18%
- Cellular 10%
- Complement 2%

Frequency of SCID
- Italy 1:77,00
- Japan 1:200,00
- Switzerland 1:54,000
- Sweden 1:55,000
- US 1:60,00

Notarangelo LD. JACI, February 2010
About RAPID

Resource of Asian Primary Immunodeficiency Diseases (RAPID) is a web-based compendium of molecular alterations in primary immunodeficiency diseases. Detailed information about genes and proteins that are affected in primary deficiency diseases is presented along with other pertinent information about protein-protein interactions, microarray gene expression profiles in various organs and cells of the immune system and mouse studies. RAPID also hosts a tool, the mutation viewer, to predict deleterious and novel mutations and also to visualize the mutation positions on the DNA sequence, protein sequence and three-dimensional structure for PID genes. The information in this database should be useful to researchers as well as clinicians.

PIDJ Network

In an effort to elucidate the pathogenesis of PIDs and establish methods of early diagnosis and find effective treatments, RCAI formed a collaboration in 2006 with 13 universities/colleges in Japan which belong to the research team for Investigative Research on Primary Immunodeficiency Disease Syndrome, ("Ministry of Health, Labor and Welfare Survey Research Team").

http://rapid.rcai.riken.jp/RAPID
Incidence of PIDD WHO 2009 Statistics

- IgA Deficiency 1:600
- Transient hypogammaglobulinemia 1:1000
- Chromosome 22q11.2D 1:3000
- Complement deficiency 1:10,000
- SCID 1:50,000
- Common variable immunodeficiency 1:50,000
- X-linked agammaglobulinemia 1:100,000
- Chronic granulomatous disease 1:150,000
CLINICAL ALGORITHM

SENTINEL ORGANISMS
- Bacterial
- Viral
- Fungal
- Parasitic

RECURRENT INFECTIONS
- Bacterial Sinopulmonary
- Bacterial Cellulitis/Abcess
- Bacterial Sepsis/Meningitis
- Viral Respiratory
- Viral Cutaneous
- Fungal Mucocutaneous
- Recurrent Fever Without Infection

CLINICAL FEATURES
- Bone Abnormalities
- Growth Abnormalities
- Cutaneous Features
- Facial Dysmorphology
- Neurologic Abnormalities
- Gastrointestinal Abnormalities
- Hematologic Abnormalities
- Endocrine Abnormalities
- Pulmonary Disease
- Syndromes

AUTOIMMUNE
- Cytopenias
- Arthritis
- Vasculitis
- Granulomas
- SLE
- IBD
- HUS
- Sjogren

DISEASES WHICH MAY REQUIRE HSCT
- SCID
- XL Hyper IgM
- Wiskott Aldrich
- IPEX
- XLP
- Primary HLH
- Chediak Higashi
- LAD 1
- CGD
- JPN-Gamma & Defects
- 22q11.2 Deletion (Complete DiGeorge)

Immunodeficiencysearch.com
Severe Combined Immune Deficiency

- SCID describes a primary immune deficiency disorder that is associated with profound T cell dysfunction and humoral (antibody) deficiency
- Over 15 genetic mutations or enzymatic deficiencies have been described in association with SCID
- Children with SCID appear normal at birth
- Illness typically begins as passively acquired maternal antibody (IgG) wanes between 3 and 6 months of age
- Early identification is critical to allow for optimal correction of this disorder
- Diagnosis is a true immune emergency
SCID Presentation

- Uniformly fatal by 12-15 months of age
- Early onset of persistent or fatal viral and fungal disease
  - Adenovirus, Rotavirus, RSV, CMV, EBV, Parainfluenza
  - Candida, P jirovecii (PJP)
- Recurrent bacterial infections
  - Pneumonia, sinusitis, otitis
- Acquisition of illness from live viral vaccines
  - MMR, Varicella
- Graft versus host disease
  - Maternal cells or cells from blood transfusions
  - CD4+ infiltrates in skin, hepatic cells, lungs, GI tract
Other potential clinical clues

*Absent Thymic Shadow on lateral CXR

Pneumocystis pneumonia
Severe Combined Immune Deficiencies

- T-cells –
  - B-cells –
    - NK-cells –
    - NK-cells +
  - B-cells +
    - NK-cells –
    - NK-cells +
- T-cells + (clonal)
  - B-cells low
  - NK-cells +

Reticular dysgenesis
- ADA deficiency
- Rag 1 and 2 deficiency
- Rag 1 and 2 recombination deficiency
- JAK3 deficiency
- $\gamma_c$ - chain deficiency
- IL-7R$\alpha$ deficiency
Ommenn Syndrome
<table>
<thead>
<tr>
<th>Type of SCID</th>
<th>Gene</th>
<th>T cells</th>
<th>B cells</th>
<th>NK cells</th>
<th>Function</th>
<th>Autoimmune</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-B+NK-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-SCID</td>
<td>Common cytokine receptor γ chain IL2RG</td>
<td>low</td>
<td>nil</td>
<td>low</td>
<td>absent</td>
<td>no</td>
<td>50% of SCID. Few patients present late. Common gamma chain for IL-2, IL-4, IL-7, IL-9, IL-15 affected.</td>
</tr>
<tr>
<td>JAK3</td>
<td>JAK 3</td>
<td>low</td>
<td>nil</td>
<td>low</td>
<td>absent</td>
<td>no</td>
<td>8% of SCID. May have nil ALC. One kindred with a mild phenotype has been identified.</td>
</tr>
<tr>
<td>CD45</td>
<td>CD45</td>
<td>low</td>
<td>Nil or increased</td>
<td>lowish</td>
<td>absent</td>
<td>no</td>
<td>Pan cytopenia a feature. γδT cells normal.</td>
</tr>
<tr>
<td>T-B+NK+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLH Def</td>
<td>Several genetic types-due to transcription factors</td>
<td>CD4 very low</td>
<td>nil</td>
<td>nil</td>
<td>Low but not absent</td>
<td>common</td>
<td>AKA bare lymphocyte syndrome; ALC often nil</td>
</tr>
<tr>
<td>IL-7Ra</td>
<td>IL-7Ra</td>
<td>low</td>
<td>nil</td>
<td>nil</td>
<td>absent</td>
<td>no</td>
<td>10% of SCID. Rare Omenn’s.</td>
</tr>
<tr>
<td>CD3γ</td>
<td>CD3γ</td>
<td>Nil by CD2, low by CD3</td>
<td>nil</td>
<td>nil</td>
<td>Low but not absent</td>
<td>common</td>
<td>IgG2 subclass deficiency. CD8 cells more decreased. Normal antibody responses to protein antigens</td>
</tr>
<tr>
<td>CD3ε</td>
<td>CD3ε</td>
<td>Nil by CD2, low by CD3</td>
<td>nil</td>
<td>nil</td>
<td>low</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>CD35</td>
<td>CD35</td>
<td>Low</td>
<td>Nil</td>
<td>Nil</td>
<td>Absent</td>
<td>?</td>
<td>No γδT cells</td>
</tr>
<tr>
<td>CD3ε</td>
<td>CD3ε</td>
<td>Low, CD8 decreased</td>
<td>Nil</td>
<td>Nil</td>
<td>Low</td>
<td>No</td>
<td>Nil immunoglobulin levels, no response to vaccines</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>ZAP-70</td>
<td>Ni but no CD8</td>
<td>nil</td>
<td>nil</td>
<td>Absent</td>
<td>Ni ALC, ni 2° lymphoid structures, nil thymus size, nil humoral immunity</td>
<td></td>
</tr>
<tr>
<td>Lck</td>
<td>Lck</td>
<td>About 300/mm³ with CD4 more decreased</td>
<td>nil</td>
<td>About 50% of nil</td>
<td>Low</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Trichothiodystrophy</td>
<td>XPD</td>
<td>Low CD4</td>
<td>Ni</td>
<td>Nil but poor function</td>
<td>Poor</td>
<td>?</td>
<td>Brittle hair, retardation, ichthyosis</td>
</tr>
<tr>
<td>OARA11</td>
<td>ORA11</td>
<td>Nil</td>
<td>Nil</td>
<td>Low</td>
<td>Low</td>
<td>?</td>
<td>Ni immunoglobulin levels, no response to vaccines. Myopathy, retardation, ectodermal dysplasia in one patient</td>
</tr>
</tbody>
</table>
Other T Cell Disorders

- **DiGeorge Syndrome, 22q11.2 deletion syndrome**
  - Clinical features:
    - Dysmorphic facies (micrognathia)
    - Hypocalcemia (lack of parathyroids)
    - Depressed T-cell immunity (absent thymus)
    - Congenital heart disease
  - Presents in first few days of life (tetany)
  - Diagnosed immediately by lateral chest x-ray (absence of thymic shadow)
  - Defect in embryogenesis, 3rd and 4th pharyngeal pouches
Other T Cell Disorders

- **Idiopathic CD4 Lymphocytopenia**
  - Low CD4 count and increased risk of fungal/protozoal infections
  - Inheritance pattern not clear
- **Wiskott-Aldrich Syndrome (X-linked disorder)**
  - Thrombocytopenia
  - Eczema
  - Infection
- **Ataxia-Telangiectasia**
  - Infection
  - Ataxia
  - Telangectasias
  - Risk of carcinoma and lymphoma/leukemia
Morbidity/Mortality in SCID/T Cell Disorders

- **SCID**
  - Fatality by 2 years of age without corrective intervention, e.g., HSCT, gene therapy, ERT
- **DiGeorge Syndrome**
  - Fatality by 2 years of age without corrective intervention, e.g., thymic transplant, MRD HSCT
- **WAS**
  - 13% with cancer risk; poor treatment outcome
- **Ataxia-telangiectasia**
  - Cancer risk in affected and heterozygous females
Treatment/Prevention Options in PIDD SCID or T Cell Disorders

• Prevention Therapy
  – Live viral vaccine avoidance
  – Irradiation of blood products to prevent graft versus host disease
  – Antibiotic prophylaxis therapy
  – Intravenous Ig supplementation

• Curative options
  – Hematopoetic Stem Cell Transplantation
  – Gene Therapy
  – Enzyme Replacement Therapy
Outcome Data from HSCT for SCID
Texas Children’s Hospital

- Survival of SCID patients post-transplant at 1 yr:
  - 10/10 (100%) for Matched Related Donor
  - 12/17 (72%) for MisMatched Related Donor/Matched Unrelated Donor with conditioning
  - 13/21 (62%) for MisMatched Related Donor, no conditioning

- Barriers to long-term survival were delay in diagnosis, pre-HSCT life-threatening infection, failure to engraft, and chronic GVHD

- Early outcomes and educational objectives of non-conditioned vs conditioned cohorts appear equal
State Map for SCID Screening Update
February 2013

Subject map showing the states' screening status for SCID.

- **Screening**
- **Selected Populations**
- **Pilots/Screening in 2013**
- **No Screening**
Early SCID diagnosis affects outcomes

Comparison of infant mortality between those groups of neonates who were not tested ($n = 138$, left) and tested ($n = 20$, right) for SCID. Testing was performed only if an affected relative’s SCID diagnosis had made parents and medical providers aware of the risk. Proportion of deceased infants is shaded in each pie chart. Proportion of deceased infants is shaded in each pie chart. 
Puck Clin Immunol. 2011

\[p = 0.026\ (\text{Fisher’s Exact, 2-sided})\]
Wisconsin Experience

- Three years of screening: 207,696 infants
- Seventy-two full term infants had abnormal TREC assay (low TREC and normal β-actin)
- Nine had abnormal on second testing due to prematurity or low β-actin
- Thirty-eight had normal T cell counts by flow cytometry
- Thirty-three were found to have T cell lymphopenia (TCL)
  - 19 - secondary causes
  - 5 – reversible TCL
  - 4 – 22q11.2 deletion syndrome
  - 5 – SCID/severe TCL

<table>
<thead>
<tr>
<th>Case no.</th>
<th>TREC</th>
<th>CD3 (naive)</th>
<th>B cell</th>
<th>NK cell</th>
<th>Mito</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. RAC2</td>
<td>0,4,0</td>
<td>2869 (2353)</td>
<td>166</td>
<td>291</td>
<td>87%</td>
</tr>
<tr>
<td>2. ADA</td>
<td>0,0,0</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>3. T⁻B⁻NK⁺</td>
<td>0,0,0</td>
<td>70 (49)</td>
<td>42</td>
<td>752</td>
<td>3%</td>
</tr>
<tr>
<td>4. T⁻B⁺NK⁺</td>
<td>0,4,3</td>
<td>411 (201)</td>
<td>1342</td>
<td>346</td>
<td>19%</td>
</tr>
<tr>
<td>5. T⁻B⁺NK⁺</td>
<td>0,0,0</td>
<td>406 (280)</td>
<td>263</td>
<td>956</td>
<td>47%</td>
</tr>
</tbody>
</table>

Verbsky, Thakar, Routes. JACI March 2012
## California experience

### First Year California NBS for TRECS

| More than 500,000 births screened |
| DNA amplification failures, <0.08%, requiring second heel stick* |
| 84% from neonatal intensive care units |
| 56% from infants who were <1500 g at birth |
| 44% had the failed sample obtained from an intravenous line |
| Fifty infants had 2 DNA amplification failure results or a positive result (0.01% of births), requiring complete blood cell count and lymphocyte analysis by using flow cytometry |
| Twenty of these (40%) had low T-cell numbers confirmed |

**Diagnoses among infants with low T-cell numbers**

**Six SCID†**
- Two IL-7 receptor defects
- Two RAG1 defects
- Two Common γ-chain defects
- **One Omenn syndrome‡ with RAG2 defect**

Three SCID variants with no known gene defect

Four Syndromes associated with T lymphocytopenia
- Three DiGeorge syndrome (1 complete)
- One Trisomy 21

Six secondary T lymphocytopenia
- Two gastroschisis
- One gastrointestinal atresia
- Three prematurity

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### Low or absent TRECS and <1500 T cells/μl

I. **Typical SCID** (see genotypes in Table II): defined as <300 autologous T cells/μL and <10% of normal proliferation to the mitogen PHA

II. **Leaky SCID** caused by incomplete (hypomorphic) mutation or mutations in a typical SCID gene with 300 to 1500 T cells/μL and impaired but not absent (10% to 30% of normal) proliferation to PHA

III. **Variant SCID** with no defect in a known SCID gene and 300 to 1500 T cells/μL that demonstrate impaired function

IV. **Syndromes with variably affected cellular immunity that might be severe**
- Complete DiGeorge syndrome*
- Partial DiGeorge syndrome with low T-lymphocyte numbers*
- **CHARGE syndrome***
- Jacobsen syndrome*
- Trisomy 21*
- RAC2-dominant interfering mutation*
- **DOCK8-deficient hyper-IgE syndrome†**
- Cartilage-hair hypoplasia

V. **Secondary T lymphocytopenia**
- Neonatal cardiac surgery with thymectomy*
- Neonatal leukemia*
- Gastroschisis*
- Third spacing*
- Extreme prematurity (resolves to normal with time)*
- Possibly severe prenatal HIV disease (hypothesized but not observed to date)

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Puck JACI 2012
Newborn Screening for SCID in the US

- Over 2.1 million US infants have been screened
- Number of identified cases: 29
- Number of syndromic patients (DiGeorge, etc) with low T cells has been 43
- Number of secondary low T cell findings (congenital heart disease, third space losses, etc): 28 cases
- The US predicted rate of SCID averaged 1:60,000 (range of 1:51,924 to 1:69,237)

Notarangelo L, ESID 2012 Florence, Italy
SCID Screening Marker: T cell receptor excision circles (TREC)

- TRECs are pieces of DNA extruded during intrathymic T cell receptor gene rearrangement
- PCR can identify TRECs by real time PCR of DNA in dried blood spots
- Absent TRECs suggests profound T cell depletion
- Identifies most mutations associated with SCID and other T cell deficiencies
- Newborns and infants have the highest number of circulating TRECs
T cell Selection in the Thymus

- T cells circulating in periphery have undergone rigorous selection in the thymus
- During thymus development, T cells express CD3 protein and TCR
- TCR gene segment recombination provides diverse T cell repertoire

A Carpenter. Nature Immunology. Sept 2010
T cells and Formation of TRECs

(Touek et al. Nature 1998)
TREC Assay

• Assay is valid only if collected specimen has adequate DNA content
  – Measured variably in differing assays as actin or DNaseP

• DNA is extracted from Guthrie Card
  – PCR performed and reported as TREC numbers/whole blood

• In the Texas assay, >250 TREC/ml whole blood will represent a normal assay
Authority for Consideration of SCID with Newborn Screening?

• Recommendation for SCID to be added to routine newborn screening panel approved by the Secretary’s Advisory Committee on Heritable Disorders of Newborns and Children in 2010

• Subsequently approved by the Secretary of Health and Human Services

• 14 US States or Territories or Nations currently screen for SCID

• Texas began newborn screening for SCID December 2012
## SCID Implementation Project: Milestones

<table>
<thead>
<tr>
<th>MAR</th>
<th>APR</th>
<th>MAY</th>
<th>JUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approval to add SCID to NBS Panel</td>
<td>• Purchasing for instruments, consumables, furniture</td>
<td>• Finalized SOW for LIMS upgrade</td>
<td>• Posted 2 lab FTEs and hired 3 temps</td>
</tr>
<tr>
<td>• Identified capital authority and funds</td>
<td>• A600 building move</td>
<td>• Approval to hire FTEs</td>
<td>• Started receiving instruments/consumables</td>
</tr>
<tr>
<td>• Finalized specifications for building</td>
<td>• Conference calls with immunologists and HL7 sites</td>
<td>• Drafted ACT and FACT sheets</td>
<td>• Immunologists meeting</td>
</tr>
<tr>
<td>• Coordinated with vendors for LIMS and HL7 changes</td>
<td>• Discontinued SCID pilot study</td>
<td>• Acceptance of Jeffrey Modell Foundation offer</td>
<td>• Complete algorithm for laboratory and CCC for PE SSD</td>
</tr>
<tr>
<td>• Stakeholder notification</td>
<td></td>
<td></td>
<td>• Final Design from architects</td>
</tr>
</tbody>
</table>

Provided by Rachel Lee, Biochemistry & Genetics Branch, DSHS
SCID Implementation Project: Milestones

**JUL**
- Continue Post/ Hire FTEs (lab and CCC)
- Evaluate reagents, calibrators, and protocol

**AUG**
- Continue Receiving and Purchasing of Equipment and Supplies
- Test HL7 messaging with hospitals
- First FTE hired, sent to CDC for training
- Building Construction starts

**SEP**
- Continue post/hire FTEs
- Technical Training in NY
- Start validating available LIMS upgrades including instrument interfaces and follow-up algorithm
- Start assay validation

**OCT**
- Complete Building Retrofit
- Start instrument installation, optimization, and training
- Start and complete instrument validation and ramp-up
- HL7 end user validation
- Full lab staff hired and trained
- Validation studies write-up and approval
- SOPs write-up and approval

**NOV**
- Complete assay validation
- Complete instrument installation, optimization, and training
- Go-Live with full LIMS functionality and HL7 messaging
- Complete LIMS upgrades validation

**DEC**
- Go-Live with full population SCID screening
SCID Newborn Screening in Texas

• Uses current dried blood spot specimen collection methodology
• Blood punch performed and by use of PCR, DNA amplification occurs to identify a biomarker of naïve T cells (TRECs)
Timeline for Performance and Reporting of SCID NBS

- Specimen arrives.
- Specimen accessioned.

**Day 1**
- Specimen punched.
- Data entry begins.
- Testing begins for all disorders except Biotinidase Deficiency (BIOT).
- DNA extraction completed.

**Day 2**
- Data entry is completed.
- Testing begins for BIOT.

**Day 3**
- Testing completed for the most time sensitive disorders.
- Clinical Care Coordination contacts provider if have out-of-range results.
- RT-PCR completed. Retests punched and extracted.

**Day 4**
- RT-PCR retests completed.
- Results for remaining disorders are released, including SCID.
- Clinical care coordination contacts provider if have out-of-range results for remaining disorders.
- DNA testing (M-F) for Galactosemia and Cystic Fibrosis, if specimen is out-of-range.

**Day 5**
- Galactosemia & Cystic Fibrosis DNA results are sent to Clinical Care Coordination.
- Result report is printed, sent to mailroom, and available online.

Hemoglobinopathy and MCAD DNA testing performed in weekly batches.

Provided by Rachel Lee, Biochemistry & Genetics Branch, DSHS
Texas Department of State Health Services  
LABORATORY SERVICES SECTION  
CLIA #46D0680644  
CONFIDENTIAL LABORATORY REPORT

File Copy

CLINICS OF NORTH TEXAS - 24330394  
ATTN: LABORATORY  
501 MIDWESTERN PKWY EAST  
WICHITA FALLS, TX 76302

NEWBORN SCREENING REPORT

Patient's Name:  
First name Last name  
Mother's Name:  
Mom First Mom last  
Date Of Birth:  
01/01/900  
Medical Record:  
77716900  
Birth Weight:  
3,080 grams  
Race/Ethnicity:  
WHITE  
Sex:  
MALE  
Birth Order:  
Feed:  
Breast Milk Only  
Status:  
NORMAL

Laboratory Number:  
2012 111 5183  
Form Serial No:  
11-0270754  
Date Collected:  
04/18/2012  
Date Received:  
04/20/2012  
Date Reported:  
04/25/2012

Test:  
2ND TEST (7 DAYS OR OVER)

Mother's Address:  
123 Main st  
Yclea, XR 12346

Mother's Telephone:  
(940) 123 - 4567

Physician's Name:  
Dr. Raymond

Physician's Telephone:  
(940) 123 - 4567

NORMAL SCREEN

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Screening Result</th>
<th>Analyte</th>
<th>Analyte Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acid Disorders</td>
<td>Normal</td>
<td>T4</td>
<td>Normal</td>
</tr>
<tr>
<td>Fatty Acid Disorders</td>
<td>Normal</td>
<td>TSH</td>
<td>Normal</td>
</tr>
<tr>
<td>Organic Acid Disorders</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXALOSIS</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIOTINIDASE DEFICIENCY</td>
<td>Normal</td>
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<td></td>
</tr>
<tr>
<td>HYPOTHYROIDISM</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAH</td>
<td>Normal</td>
<td></td>
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<tr>
<td>HEMOGLOBINOPATHIES</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYSTIC FIBROSIS</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The newborn screen identifies newborns at increased risk for specified disorders. The reference values for all screened disorders are Normal. Analyte results are only listed for abnormal disorders screening results. The recommended collection time period for the testing methodologies has been designed to minimize the number of false negative and false positive results in newborns and young infants. When the newborn screen specimen is collected below 24 hours of age or on older children, the test may not identify some of these conditions. If there is a clinical concern, diagnostic testing should be initiated. Findings that are uninterpretable are reported as uninterpretable.

The SMH TREC was performed to fulfill routine newborn screening requirements. The test was evaluated and its performance characteristics determined by DBI III. The test was not approved by the US Food and Drug Administration (FDA). The FDA has determined that such approval and necessary Performance characteristics are verified in the testing laboratory.

1. Disorders Screened: AMINO ACID DISORDERS: Argininosuccinic Aciduria (ASA), Citrullinemia (CT), homocystinuria (HCY), Maple Syrup Urine Disease (MUSUD), Phenylketonuria (PKU); Cystinuria Type 1 (CYS1), FATTY ACID DESORDERS: Organic Acid Urine, Organic Aciduria, Organic Aciduria, Organic Aciduria, Organic Aciduria, Organic Aciduria, Organic Aciduria, Organic Aciduria, Organic Aciduria; TRYPOLIDINE DEFICIENCY (TDP), Trinucleotide Triphosphatase D (TTPD), Long-Chain Acyl-CoA Dehydrogenase Def (LCAD), Medium-Chain Acyl-CoA Dehydrogenase Def (MCAD), Very Long-Chain Acyl-CoA Dehydrogenase Def (VLCAD), Organic Acid Deficiency; 3-METHYLMALONIC ACIDURIA (MMA), Multiple Carboxylase Def (MCAD), Propionic Acidemia (PA),: BIOTINIDASE DEFICIENCY, CONGENITAL ADRENAL HYPERPLASIA (CAH), CONGENITAL HYPOPHOSPHATEMIA, CYSTIC FIBROSIS, IDIOPATHIC HYPOGLYCEMIA, HOMOCYSTINURIA, HYPOGLYCEMIA, INHERITED IMMUNE DEFICIENCY DISORDERS.

For more information, please refer to http://www.dshs.state.tx.us/lab/newbornscreening.shtml
### Screening Result Notes

<table>
<thead>
<tr>
<th>Screening Result</th>
<th>Analyte</th>
<th>Analyte Result</th>
<th>Screening Result Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>TREC</td>
<td>Undetectable or very low</td>
<td>Probable severe combined immunodeficiency or other immunodeficiency. Recommend referral to a clinical immunologist.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Undetectable or very low number of T-cell receptor excision circles (TREC). Possible severe combined immunodeficiency or other immunodeficiency. Please repeat the newborn screen.</td>
</tr>
</tbody>
</table>

Provided by Rachel Lee, Biochemistry & Genetics Branch, DSHS
How Many SCID Children are Expected to be Identified in Texas?

- With a birth rate of about 350,000/year in Texas, 10 – 12 children with SCID diagnosis may be detected.

- The majority of genetic forms of SCID (>90%) are associated with early lymhopenia and will be detected by the TREC assay.
  - X-linked SCID (Bubble Boy SCID) representing >50% of all SCID.
  - Autosomal Recessive SCID.
  - Enzymatic Deficiencies associated with SCID.
Texas TREC Assay

- Assay is valid only if collected specimen has adequate DNA content
  - Measured variably in differing assays as actin or RNaseP
  - RNaseP is measured as the H1 component of human ribonuclease gene and serves as a genomic reference in the Texas TREC assay
    - In the Texas assay RNaseP count ≤32 is established cutoff
      - Similarly used in other States (NY, MA)
- DNA is extracted from Guthrie Card
  - PCR performed and reported as TREC numbers/mL whole blood
    - In the Texas assay, >250 TREC/mL whole blood will represent a normal assay for infants over 2000 grams
    - For children <2000 grams, >200 TREC/mL whole blood currently represents a normal assay
Validation Assays for TREC in Texas

• All BW TREC
  – Median 1159 TREC/mL whole blood
  – 1% 243 TREC/mL whole blood

• TREC in VLBW (<2000 grams)
  – Median 864 TREC/mL whole blood
  – 5% 200 TREC/mL whole blood
<table>
<thead>
<tr>
<th>Initial Screen</th>
<th>RT PCR Result</th>
<th>Recorded Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC ≤ 250 or RNaseP CT &gt;32</td>
<td>Retest (double punch)</td>
<td></td>
</tr>
<tr>
<td>TREC ≥250 and RNaseP CT ≤32</td>
<td>Normal TREC</td>
<td></td>
</tr>
<tr>
<td>Retest</td>
<td>Average TREC &gt; 200</td>
<td>Normal TREC</td>
</tr>
<tr>
<td>Average TREC &gt; 200 and RNaseP CT &gt;32</td>
<td>Indeterminate</td>
<td></td>
</tr>
<tr>
<td>Average TREC=0 and RNaseP CT ≤32</td>
<td>Abnormal-Undetectable TREC</td>
<td></td>
</tr>
<tr>
<td>0 &lt; Average TREC ≤ 150 and RNASE CT ≤32</td>
<td>Abnormal-Very Low TREC</td>
<td></td>
</tr>
<tr>
<td>150 &lt; Average TREC ≤ 200 and RNaseP CT ≤32</td>
<td>Abnormal-Very Low TREC for BW≥2000g Borderline-Low TREC for BV&lt;2000g</td>
<td></td>
</tr>
</tbody>
</table>
Non-immune Conditions May Cause Indeterminate or Abnormal TREC Test Results

• About 0.05 – 0.08% of all performed tests may result in an abnormal test
• Most abnormal testing results occurred in premature infants or sick infants in pediatric or neonatal intensive care units
  • 84% of such tests were reported from infants with intravenous lines in NICU/PICU settings
  • 56% had birth weights under 1500 grams
  • Repeat testing identified normal values in such infants

Puck, JACI 2010 and 2012
Other Disorders with T cell lymphopenia that may be Identified by SCID NBS

- Syndromes
  - DiGeorge Syndrome
  - Wiskott-Aldrich Syndrome
  - CHARGE syndrome
  - Trisomy 21
  - Dock 8 Deficiency
    - Autosomal recessive HyperIgE syndrome
Secondary T cell losses

• Disorders associated with lymphocyte loss may have abnormal TREC testing
  • Congenital lymph disorders
    – Hennekam syndrome (GI, resp, skin losses)
    – Lymphoangiomatosis (pulmonary losses)
  • Surgical procedures associated with chylous losses
    – Cardiac surgical correction/Fontan
    – Chylothorax
  • Gastrointestinal disorders associated with lymph loss
    – GI Atresias associated with protein losing enteropathy
    – Lymphangiectasia
Two Examples
Undetectable TRECS

- 2 week old with undetectable TREC x 2

T-B+NK- SCID

ALC 1417

T&B lymphocyte study:
- T cells: CD3 0.5%, CD4 0.5%, CD8 0.1%
- B cells: CD19: 96.6%
- NK cells: CD56, CD16+: 2.3%
Pedigree of the patients with XCID

Schmalstieg. Molecular Genetics and Metabolism 2002
Abnormal Low TREC

- Full term vaginal delivery; Normal Prenatal testing
- First male infant to G1P1 mother
- Heart Murmur on exam

**Blood Test Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>8.73</td>
</tr>
<tr>
<td>RBC</td>
<td>2.95</td>
</tr>
<tr>
<td>HGB</td>
<td>14.0</td>
</tr>
<tr>
<td>HCT</td>
<td>39.3</td>
</tr>
<tr>
<td>MCV</td>
<td>99.5</td>
</tr>
<tr>
<td>MCH</td>
<td>35.4</td>
</tr>
<tr>
<td>MCHC</td>
<td>35.6</td>
</tr>
<tr>
<td>RDW/VWC</td>
<td>14.7</td>
</tr>
<tr>
<td>RDW/SD</td>
<td>53.2</td>
</tr>
<tr>
<td>Platelet</td>
<td>209</td>
</tr>
<tr>
<td>MPV</td>
<td>Platelet size variance. See smear review.</td>
</tr>
<tr>
<td>Differential Type</td>
<td>MAN</td>
</tr>
<tr>
<td>Seg%</td>
<td>12.6</td>
</tr>
<tr>
<td>Band%</td>
<td>0.8</td>
</tr>
<tr>
<td>Lymph%</td>
<td>69.0</td>
</tr>
<tr>
<td>Reactive lymphocytes noted on smear review</td>
<td></td>
</tr>
<tr>
<td>Mono%</td>
<td>9.2</td>
</tr>
<tr>
<td>EOS%</td>
<td>7.6</td>
</tr>
<tr>
<td>Meta%</td>
<td>0.8</td>
</tr>
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</table>

**Cell Counts**

<table>
<thead>
<tr>
<th>CD3+TCell Pcent</th>
<th>CD3+TCell Numbr</th>
<th>CD3+CD4+Pcent</th>
<th>CD3+CD4+Numbr</th>
<th>CD3+CD8+Pcent</th>
<th>CD3+CD8+Numbr</th>
<th>CD19+BCell Pcent</th>
<th>CD19+BCell Numbr</th>
<th>CD3-CD56CD16+Pcent</th>
<th>CD3-CD56CD16+Numbr</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>2701</td>
<td>31.0</td>
<td>1861</td>
<td>11</td>
<td>660</td>
<td>25</td>
<td>1501</td>
<td>28</td>
<td>1681</td>
</tr>
</tbody>
</table>

**PHA Test**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHA 1 ug/mL</td>
<td>280590</td>
</tr>
<tr>
<td>PHA 1 ug/mL Index</td>
<td>208.69</td>
</tr>
<tr>
<td>PHA 1 ug/mL</td>
<td>177903</td>
</tr>
<tr>
<td>PHA 1 ug/mL Index</td>
<td>132.68</td>
</tr>
<tr>
<td>CON A 50</td>
<td>288058</td>
</tr>
<tr>
<td>CON A 50 Index</td>
<td>214.22</td>
</tr>
<tr>
<td>CON A 5</td>
<td>248726</td>
</tr>
<tr>
<td>CON A 5 Index</td>
<td>185.11</td>
</tr>
<tr>
<td>PWM 100</td>
<td>190038</td>
</tr>
<tr>
<td>PWM 100 Index</td>
<td>141.66</td>
</tr>
<tr>
<td>PWM 10</td>
<td>58948</td>
</tr>
<tr>
<td>PWM 10 Index</td>
<td>44.63</td>
</tr>
</tbody>
</table>

ALC 6000
Thymus

Normal Screen

Abnormal Low Screen

22.q11.2 Deletion
Early Diagnosis SCID: Interventions that Save Lives

• Minimizing exposure to pathogens
  – Avoidance of live viral vaccines
  – Avoidance of exposure to sick individuals

• Provision of waning/absent immunoglobulin/antibody

• Avoidance of transfusion reactions
  – Simple red cell irradiation prior to transfusion minimizes risk for graft versus host disease

• Early detection and treatment of graft versus host disease and/or infection

• When possible correction of the underlying immune defect
How Quickly Should Children with an Abnormal NBS SCID be Referred for Specialty Assessment?

• Once you are notified of an abnormal NBS SCID screen, immediate referral is recommended, no less than 2 days.

• The preferred referral physician should be a pediatric immunologist.

• DSHS can provide primary physicians with a listing of pediatric immunologists across each Region of the State who have expertise and are willing to assess children with abnormal testing.

• Referrals should conform with local patterns of care access and consider both payor limitations and parental choice.
Testing for an infant with an abnormal SCID screening test?

- A simple CBC with differential and platelet count will be helpful
  - Parameters to review include
    - Absolute lymphocyte count
    - Absolute neutrophil count
    - Platelet count

- CXR (PA/Lateral)
  - This test can be performed by the immunologist accepting care for the child.
  - Consider performance by primary physician if there is another clinical indication
    - Cough
    - Heart Murmur
Special Care Plans for Children With Abnormal TRECS While Awaiting Specialty Assessment

• Emphasize adequate nutrition
  – Many physicians may consider avoidance of breast feeding to avoid CMV exposure
• Immediate hospitalization is not typically required for well appearing infants
• Avoidance of known ill individuals and crowds is important
  – Avoid daycare placement
• Live viral vaccines should be AVOIDED
  – NO Rotavirus, MMR, Varicella vaccines
• If blood transfusions are immediately needed
  – Use CMV negative, irradiated blood products
What tests are likely to be performed by specialists on children with abnormal TREC testing at birth and 2 weeks?

- CBC with differential and platelet count
- Serum immunoglobulin/antibody levels
  - IgG, IgA, IgM, IgE
- Lymphocyte subset analysis
  - Special attention to mature T lymphocyte, B lymphocyte and Natural Killer cell markers
- Lymphocyte proliferation analysis
  - In vitro responses to plant proteins and dependent upon age antigens that the child has been exposed to (diphtheria, tetanus, etc)
- Imaging is likely to be performed
  - Chest radiograph and others
- Genetic testing
Benefits of Genetic Testing in SCID

• Identification of genetic mutations associated with SCID is of more than academic interest:
  – Allows genetic counseling for future pregnancies in affected families and child
  – Allows options for in utero testing of next pregnancies
  – Allows IVF options to families planning future pregnancies
  – Helps with determination of transplantation options for affected children
    • Gene therapy versus stem cell transplantation
    • Conditioning regimen
### Abnormal NBS SCID screen in Texas: December 2012 – May 2013

#### December 2012-February 2013

<table>
<thead>
<tr>
<th>Cases Diagnosed</th>
<th>Condition Types/Flow Phenoyping</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SCID / T-B+NK-</td>
<td>(1) SCID (expired)</td>
</tr>
<tr>
<td>0</td>
<td>Leaky SCID/Omenn Syndrome/ T-B+NK-</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Variant SCID / (T-B+NK+) SCID</td>
<td>(1) SCID-IL-7Ra Chain Defect</td>
</tr>
<tr>
<td>6</td>
<td>Syndromes with T cell impairment / (T-B+NK+)</td>
<td>(6) DiGeorge Spectrum</td>
</tr>
</tbody>
</table>
| 18               | Secondary T cell lymphopenia other than preterm alone / (other) | (5) Trisomy-21 (1 with Hydrops Fetalis)
(1) Lymphangiectasia of bowel
(1) Tetralogy of Fallot and other anomalies
(7) Pulmonary Atesia and other anomalies
(4) Unspecified Cardiac Anomaly |

**Total** 26

#### March 2013-May 2013

<table>
<thead>
<tr>
<th>Total number of specimens screened</th>
<th>Total number of initial newborn specimens screened</th>
<th>Total number of specimens with abnormal undetectable, borderline, and abnormal (very low) results reported for SCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>178,007</td>
<td>91,407</td>
<td>548</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases Diagnosed</th>
<th>Condition Types/Flow Phenoyping</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SCID / T-B+NK-</td>
<td>(1) SCID X-Linked</td>
</tr>
<tr>
<td>0</td>
<td>Leaky SCID/Omenn Syndrome/ T-B-NK-</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Variant SCID/t(T-B-NK+)</td>
<td></td>
</tr>
</tbody>
</table>
| 3                | Syndromes with T cell impairment / (T-B+NK+) | (1) *T Cell Lymphopenia (not SCID)
(3) DiGeorge Spectrum |
| 43               | Secondary T cell lymphopenia other than preterm alone / (other) | (12) Cardiac Anomalies
(4) Multiple Congenital Anomalies
(3) Chylothorax
(3) Trisomy 21
(2) Trisomy 18
(2) Other Chromosomal Defects
(2) Hydrops Fetalis
(2) Chemotherapy Treatment
(2) Gastroschisis
(1) Pulmonary Hyperplasia & Other Anomalies
(1) Aciotes
(1) Lymphopenia & Congenital Anomalies
(1) Craniosynostosis
(1) Very Large Omphalocoele
(1) Kidney Problems
(1) Abdominal Perforation
(1) Liver Anomaly & Other Congenital Anomalies
(1) Intraventricular Hemorrhage
(1) Necrotizing Enterocolitis
(1) Meconium-Plug Syndrome |

| 9                | Preterm infants may have T-cell lymphopenia / (CD3 T-cells ≤ 1500 cells/μL) and no other recognizable disorder | (9) Preterm infants T-cell lymphopenia |

**Total** 56

*initially reported as “SCID-IL-7Ra Chain Defect”

---

### Referral to TCH

<table>
<thead>
<tr>
<th>Physician</th>
<th>Indeterminate</th>
<th>Borderline</th>
<th>Abn. Low</th>
<th>Undetectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCH</td>
<td>2</td>
<td>1</td>
<td>50</td>
<td>9</td>
</tr>
</tbody>
</table>

**Courtesy DSHS**
Acknowledgements

- Special thanks to the Texas Children’s Hospital/BCM team participating in the DSHS SCID NBS screening pilot and the parents/infants participating at BTGH/Houston
- Dr. Celine Hanson – Immunology, clinic chief
  - Victor Bernabe, Roslyn Donaie, Carolyn Fairchild, Terry Raburn, Drs. Sielski and Garcia-Prats and Rosa Vega
- DSHS
  - Biochemistry and Genetics Branch
  - Newborn Screening Unit
  - Dr. Debbie Freedenberg, Daisy Johnson, Ginger Scott, Kim LaBoard
- Parent advocates who worked tirelessly to promote SCID NBS in Texas
- Supporting State Agencies
  - TPS, TFPS, March of Dimes (Dr. Charleta Guillory) and others
Texas Newborn Screening Program Advances and Updates for General Pediatricians: The Latest Developments in Critical Congenital Heart Disease (CCHD) Screening

Michael E. Speer, MD
Professor of Pediatrics & Ethics
Disclosure

• “I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.” I have received royalties from UpToDate and a stipend from Houston Methodist Hospital.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Appreciation

• To Alice Gong, MD, Charleta Guillory, MD and Debra Freedenberg, MD, PhD whose dedication and work made possible and HB 740, which established CCHD screening in Texas, a reality.
Background

• Incidence of Congenital Heart Disease (CHD)
  
  - 6 to 13 per 1000 live births

  - Critical Congenital Heart Disease (CCHD)
    
    • CHD requiring intervention (i.e., surgery &/or catheter) in the 1st year of life
    
    • 25% of CHD (~2/1000 live births)
## Screening for Metabolic Disease

[http://www.health.state.mn.us/divs/phl/newborn/docs/cchd.pdf](http://www.health.state.mn.us/divs/phl/newborn/docs/cchd.pdf)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobinopathy</td>
<td>1/2,000</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/2,000</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1/4,000</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Adrenal hyperplasia</td>
<td>1/12,000</td>
</tr>
<tr>
<td>MCAD deficiency</td>
<td>1/17,000</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1/50,000</td>
</tr>
<tr>
<td>Biotidinase deficiency</td>
<td>1/100,000</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>1/100,000</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>1/150,000</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>1/180,000</td>
</tr>
<tr>
<td>Miscellaneous amino acid, fatty acid, organic acid, and lysosomal abnormalities</td>
<td>1/50,000 to &lt;1/100,000</td>
</tr>
</tbody>
</table>

Total = 1.55 /1,000 live births
Types of CCHD

- Ductal dependent systemic circulation
  - HLHS, Coarctation, IAA, Critical AS
- Ductal dependent pulmonary circulation
  - PA, PS and variants, TOF, TA
- Complex critical CHD
  - TGA, Truncus Arteriosus, TAPVR, Single ventricle
Epidemiology

• 30% of patients with critical CHD are diagnosed after birth hospitalization discharge*

• Critical CHD can precipitously present with serious and life-threatening manifestations of their cardiac disease^

• More than half of 152 neonates with missed diagnosis of CCHD during their initial birth hospitalization died#

## Diagnosis vs. Screening

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>Fewer resources needed</td>
<td>Higher detection rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More uniform approach</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Identification may be too late</td>
<td>High resource use</td>
</tr>
<tr>
<td></td>
<td>Application may be spotty</td>
<td>Adverse impact of false positives</td>
</tr>
</tbody>
</table>
Screening

- Screening valuable if:
  - Incidence is sufficient in the population
  - Therapy provided before onset of clinical manifestations results in an improved outcome
  - Screening identifies disease before symptoms
  - Acceptable sensitivity and false positive rates
  - Cost effective

CCHD detection – diagnostic

- Fetal echocardiography
  - >50% detection rates for single ventricle lesions
  - <30% for 2-ventricle
    - Highly variable, limited access

- Newborn physical exam
  - 4-5 grams of deoxygenated Hgb is needed to detect cyanosis
  - Most CCHD have mild desaturation to 80-95%
  - Harder in darker skinned babies
CCHD Screening

- **Pulse Oximetry**
  - Indirectly monitors the oxygen saturation of a patient's blood and changes in blood flow in the skin
  - Can detect mild hypoxemia without obvious cyanosis
  - Can provide continuous and immediate values
CCHD Screening

- Pulse Oximetry
  - Non-invasive
  - Easy to use and widely available
  - Cost-effective and widely used
Pulse Oximetry Screening- Evidence

- Utility of arm/leg oximetry
- 2876 newborns in WBN
  - 57 (0.02%) abnormal screen; 4 with CCHD
  - 32 with CHD
    - 85% with left heart obstructive disease and 79% of other abnormal screen

Ped Cardiol. 2002. 23: 203-409
Pulse Oximetry Screening Program Saxony, Germany

- Newborns screened: 41,445
- Protocol violation: 3
- POS pos: 54
  - False pos: 40
  - True pos: 14
- POS neg: 41,388
  - False neg: 4
  - True neg: 41,384
- PPHN: 15
  - Sepsis: 13
  - Healthy: 12

0.13%
Pulse Oximetry Screening

- Meta-analysis of pulse ox screening for CCHD in asymptomatic newborns
  - Over 220,000 NB’s
  - Overall sensitivity was 76.5%, specificity was 99.9% with a false positive rate of 0.14%

Lancet 2012;379:2459-64
Cost

- Includes*
  - Screening equipment
  - Supplies associated with screening (e.g., probes, adhesive wraps)
  - Staff time needed to perform screening and track results.

*http://www.cdc.gov/ncbddd/pediatricgenetics/pulse.html
Cost

- Estimated direct cost less than $15.00 per infant
  - Calculation of time = 10 min per child
  - Question: ? no new nursing or medical technician FTEs added

^http://www.cdc.gov/ncbddd/pediatricgenetics/pulse.html
Cost

- Does not count costs associated with diagnosis and follow-up of infants with out-of-range (positive) results

^http://www.cdc.gov/ncbddd/pediatricgenetics/pulse.html
Additional Costs

- Comparative cost of screening
  - CCHD: 8,000 cases per year in the US + 5600 false positive (0.14% x 4,000,000 births)
  - Screen will cause additional 13,600 ECHOs per year
    - Cost: ~$10,900 [13,600 x $2000/echo ÷ 8,000 + $7,500 screen cost/diagnosis] per patient diagnosed
  - Metabolic disorders: 6,400 cases per year in the US
    - Cost /screen: @110, $68,750 per diagnosis
Recommendations

- US HHS Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
  - In 2010, Committee recommended CCHD be added to the newborn uniform screening panel
  - 2011, Endorsed by Secretary of Health Kathleen Sibelius
CCHD Entities Screened

- Hypoplastic Left Heart Syndrome
- Pulmonary Atresia (with intact atrial septum)
- Tetralogy of Fallot
- Total Anomalous Pulmonary Venous Return
- Transposition of the Great Arteries
- Tricuspid Atresia
Secondary Screening Targets

- Can be just as severe but not consistently detected
  - Aortic arch atresia/hypoplasia
  - Interrupted aortic arch
  - Coarctation
  - Ebstein’s anomaly
  - Critical PS
Interested Parties in Newborn Oximetry Screening

- **Advocates**
  - Families with CHD
  - Pediatric Cardiologist

- **Possible opponents**
  - Delivery Hospitals
  - Insurance companies

- **Neutral**
  - Public Health Analysts
  - Pediatricians/Neonatologists
National Efforts

- Maryland first state to pass CCHD screening legislation
- New Jersey first state to mandate universal CCHD screening- Implemented August 31, 2011
Potential Barriers

- States have different processes
- Several programs who do not publish their experience
- Reporting/Tracking/QI
- Inadequate resources
- Limited US evidence-based research
- Resistance from some in the medical community
Potential Barriers

- Screener
  - Additional work load; Education
- Equipment
  - Probe; Machine
- Patient/Parent
  - False positives, false negatives
  - Delay in discharge
- Potential transfer to another center
- Costs and reimbursement
Association of State and Territorial Health Officials

Newborn Screening – Critical Congenital Heart Defects
Current Status

In 2013, FL appropriated $155,502 in non-recurring funds and $50,000 in non-recurring funds for the inclusion of newborn screening for CCHD into the state’s newborn screening program. However, chapter 2013-40 does not mandate newborn screening for CCHD.

Last Updated: 7/10/2013
AAP/CDC Algorithm

Child in well-baby nursery ≥ 24 hours of age or shortly before discharge if < 24 hours of age

Screen

- < 90% in right hand or foot
- 90% - <95% in right hand and foot or >3% difference between right hand and foot
- ≥ 95% in right hand or foot and ≤3% difference between right hand and foot

Repeat screen in 1 hour

- < 90% in right hand or foot
- 90% - <95% in right hand and foot or >3% difference between right hand and foot
- ≥ 95% in right hand or foot and ≤3% difference between right hand and foot

Repeat screen in 1 hour

- < 90% in right hand or foot
- 90% - <95% in right hand and foot or >3% difference between right hand and foot
- ≥ 95% in right hand or foot and ≤3% difference between right hand and foot

Positive Screen

Negative Screen

Pediatrics
Evaluation for Positive Screen

- Clinical Assessment
- Infectious or Pulmonary pathology should be excluded
- Complete echocardiogram
- Pediatric Cardiology referral as indicated
Managing the Positive Screen

“In the absence of other findings to explain hypoxemia, CCHD needs to be excluded on the basis of a diagnostic echocardiogram (which would involve an echocardiogram within the hospital or birthing center or transport to another institution)…..”

Kemper et al Pediatrics 2011
Texas Pulse Oximetry Project: A Joint Educational Initiative

- Goal: Develop an appropriate implementation strategy for screening of CCHD using pulse oximetry as a potential public health mandate
  - Develop and provide educational programs and materials
- Funding: TDSH Services’ Children’s Outreach Heart Program
- Devised and implemented Needs Assessment of clinical sites
- Developed an educational plan
  - Curriculum and educational materials
- Target: 13 facilities in South Texas and SE Texas
  - Rural hospital to the large metropolitan medical centers
- Identified a staff person at each facility to champion CCHD screening
http://neonate.net/TxPOP/