

# University of Iowa's Experience with SCID Implementation

Mary Beth Fasano, MD, MSPH  
North Dakota Newborn Screening Conference  
May 20, 2016



# Disclosures

---

- Medical consultant – Iowa SCID Newborn Screening Program

# Learning Objectives

- List non-SCID causes for an abnormal TREC on newborn screening
- Identify challenges in the evaluation of an infant with a presumptive positive SCID newborn screen

# Severe Combined Immunodeficiency

- Diverse group of inherited disorders related to mutations in genes involved in lymphocyte development
  - >20 genes identified
    - T-cell lymphopenia
    - Impaired cellular & humoral (B-cell) immunity
    - Variable deficits in NK cell number & function
  - Infants appear healthy at birth

# Timeline: SCID Newborn Screening

2007: SCID  
nominated  
to RUSP

2008:  
Wisconsin  
begins  
population  
based NBS  
for SCID

2010: DHHS  
Secretary  
endorses  
SCID NBS

September  
12, 2012  
Iowa State  
Board of  
Health  
approves  
addition of  
SCID to NBS

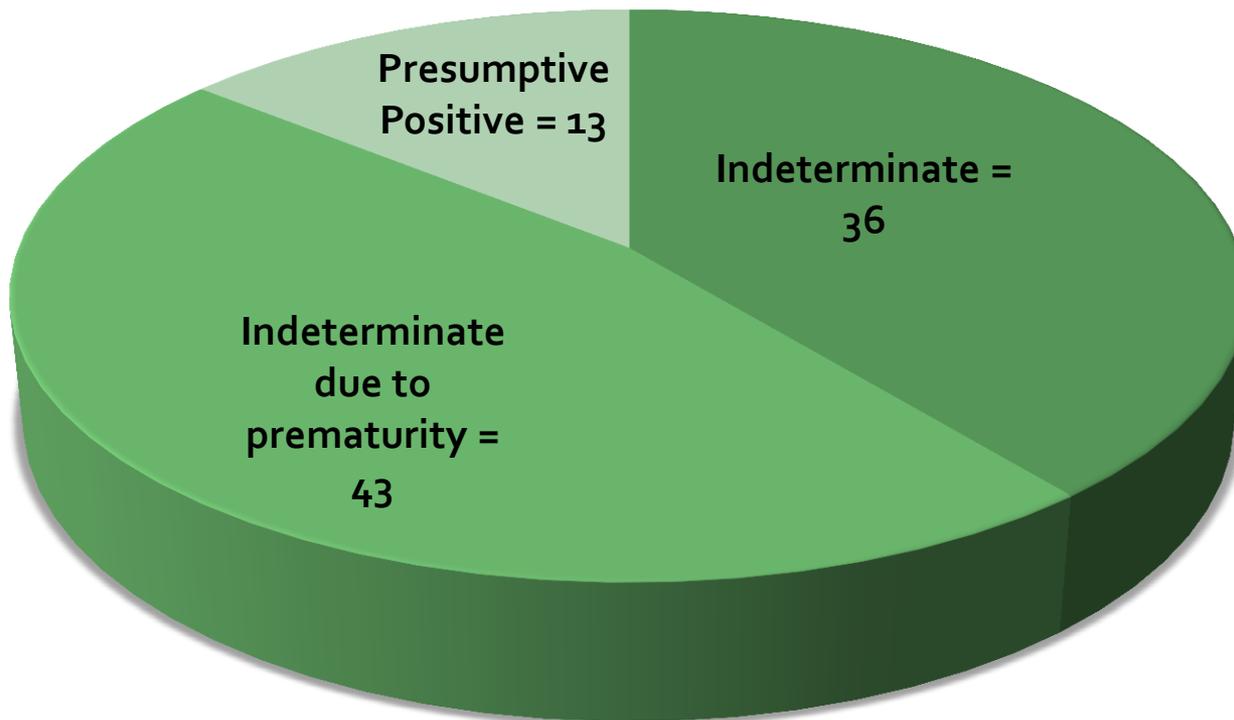
June 3, 2013:  
SCID NBS  
pilot begins  
in Iowa

June 30,  
2014: end of  
SCID NBS  
pilot in Iowa

# Iowa's Implementation Pilot

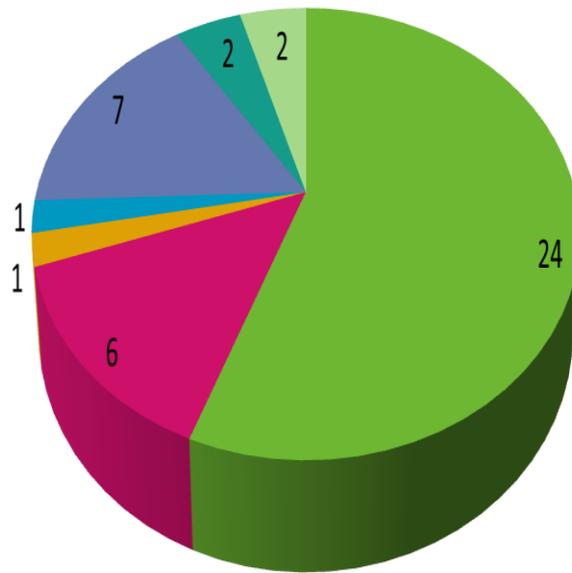
June 3, 2013 – June 30, 2014

43,930 babies screened; 92 abnormal results



# Indeterminate due to Prematurity

## Indeterminate due to Prematurity Results (43 total)



■ 2nd NBS was within normal limits (WNL)

■ 3rd NBS was WNL

■ 4th NBS was WNL

■ 6th NBS was WNL

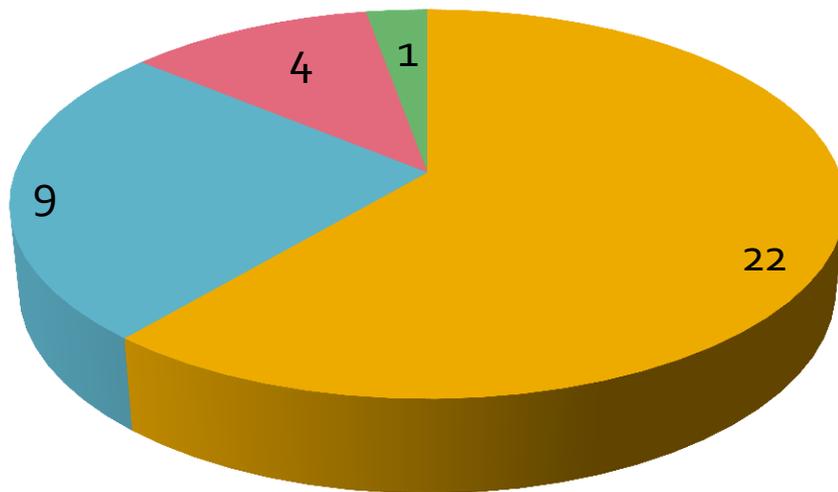
■ Prior specimen was WNL for SCID - no additional recommendations provided

■ Deceased

■ Pending diagnosis

# Indeterminate

## Indeterminate Results (36 total)



- Repeat newborn screen is within normal limits
- Repeat sample was recommended but not obtained - case closed against medical advice
- Infant had a previous within normal limits SCID newborn screen result
- Indeterminate result defaulted to flow cytometry testing - flow results were within normal limits

# Presumptive Positive (N=13 + 1)

- NBS team notifies the PCP
  - Request for 2<sup>nd</sup> tier testing & clinical information
  - Institute infection control measures
- 2<sup>nd</sup> tier testing = Flow cytometry
  - Absolute lymphocyte count & lymphocyte subsets
- Formal immune evaluation for newborns with significant T-cell lymphopenia (sTCL)

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014	Total
Infants screened	43,930
Presumptive Positive/Indeterminate <i>June 2013</i> <i>July 2013</i> <i>March 2014</i> <i>April 2014</i> <i>June 2014</i>	13/1 (0.032%) 6 1 2 2 3
Male	10/14 (71%)
Intensive Care Unit	8/14 (57%)
Infant of diabetic mother	4/14 (29%)
Hispanic	3/14 (21%)

# Lymphocyte subset analysis

- 2<sup>nd</sup> tier testing = Flow cytometry
  - NBS courier to UIHC (no weekends/holidays)
- Lymphocyte subset analysis
  - Absolute lymphocyte count
  - CD3+ T-cells (< 1500 cells/ $\mu$ l)
  - CD4+ T-cells
  - CD8+ T cells
  - CD19+ B cells
  - CD56+ NK cells
  - CD4+/CD45RA (<5% of total CD3+ T cells)

# Flow Results

- Not concerning for SCID
  - PCP contacted & infection control measures discontinued
- Significant T-cell lymphopenia concerning for SCID
  - PCP contacted & baby seen by UI Immunology within 7 days
    - Inpatient vs Outpatient
      - Family history of SCID
      - Degree of CD3 lymphopenia
      - Other co-morbidities
      - Active infection
      - Family situation

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3
- Initial = normal/repeat [CAH] = abnormal Gr B Strep respiratory infection; <b>NICU</b>	1

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3
- Initial = normal/repeat [CAH] = abnormal Gr B Strep respiratory infection; NICU	1
- Pustular melanosis	1

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3
- Initial = normal/repeat [CAH] = abnormal Gr B Strep respiratory infection; <b>NICU</b>	1
- Pustular melanosis	1
Maternal chorioamnionitis & possible drug abuse Stat <b>C/S</b> ; meconium; <b>NICU</b>	1
Stat <b>C/S</b> -prolapsed cord; hypoxic ischemic injury Gr 3 IVH, posthemorrhagic hydrocephalus; seizures; <b>NICU</b>	1*
Maternal <b>diabetic</b> cardiomyopathy, <b>obesity</b> & HTN, polyhydramnios, macrosomia <b>C/S</b> absent fetal movements; resp distress/intubated; seizures thrombocytopenia; <b>NICU</b>	1
Gestational <b>diabetes</b> & maternal <b>obesity</b>	1
Maternal <b>diabetes</b> & <b>obesity</b> ; IUGR; <b>C/S</b> – placenta accreta hypoglycemia, respiratory distress, <b>dysmorphic</b> ; <b>NICU</b>	1

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3
- Initial = normal/repeat [CAH] = abnormal; Gr B Strep respiratory infection; <b>NICU</b>	1
- Pustular melanosis	1
- Maternal chorioamnionitis & possible drug abuse; Stat <b>C/S</b> ; meconium; <b>NICU</b>	1
- Stat <b>C/S</b> -prolapsed cord; hypoxic ischemic injury; Gr 3 IVH, posthemorrhagic hydrocephalus; seizures; <b>NICU</b>	1*
- Maternal <b>diabetic</b> cardiomyopathy, <b>obesity</b> & HTN, polyhydramnios, macrosomia; <b>C/S</b> absent fetal movements; resp distress/intubated; seizures thrombocytopenia; <b>NICU</b>	1
- Gestational <b>diabetes</b> & maternal <b>obesity</b>	1
- Maternal <b>diabetes</b> & <b>obesity</b> ; IUGR; <b>C/S</b> – placenta accreta hypoglycemia, respiratory distress, <b>dysmorphic</b> ; <b>NICU</b>	1
- <b>22q11</b> ; complex <b>congenital heart dz</b> (DORV, PS, ASD, VSD); <b>PICU</b> - Mild ↓ ALC; normal T-cell function	1

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
<b>Flow not concerning for sTCL/SCID</b>	<b>11 (79%)</b>
- TREC normal by current criteria	3
- Initial = normal/repeat [CAH] = abnormal; Gr B Strep respiratory infection; NICU	1
- Pustular melanosis	1
- Maternal chorioamnionitis & possible drug abuse; Stat C/S; meconium; NICU	1
<ul style="list-style-type: none"> <li>- Stat <b>C/S</b>-prolapsed cord; hypoxic ischemic injury; Gr 3 IVH, posthemorrhagic hydrocephalus; seizures; <b>NICU</b></li> <li>- <i>Dx with <b>22q11</b> – age 6 mon; Mild ↓ ALC &amp; normal immune eval – age 9 mon</i></li> </ul>	1*
- Maternal <b>diabetic</b> cardiomyopathy, <b>obesity</b> & HTN, polyhydramnios, macrosomia; <b>C/S</b> absent fetal movements; resp distress/intubated; seizures thrombocytopenia; <b>NICU</b>	1
- Gestational <b>diabetes</b> & maternal <b>obesity</b>	1
- Maternal <b>diabetes</b> & <b>obesity</b> ; IUGR; <b>C/S</b> – placenta accreta hypoglycemia, respiratory distress, <b>dysmorphic</b> ; <b>NICU</b>	1
<ul style="list-style-type: none"> <li>- <b>22q11</b>; complex <b>congenital heart dz</b> (DORV, PS, ASD, VSD); <b>PICU</b></li> <li>- Mild ↓ ALC; normal T-cell function</li> </ul>	1

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014  
Presumptive Positives

Total = 14

Flow **concerning** for SCID

3 (21%)


Iowa SCID NBS Pilot June 3, 2013 – June 31, 2014  
Presumptive Positives

Total = 14

Flow **concerning** for SCID

3 (21%)

**Jacobsen Syndrome:** [11Mb del 11q24.2q25] (CD3 = 1637)

1

- Gestational **diabetes**, polyhydramnios, concern for Trisomy 18
- Apneic/intubated at birth; congenital pneumonia; cytopenias; **NICU**
- Normal immune work-up; mild cytopenia at age 12 mon

Iowa SCID NBS Pilot June 3, 2013 – June 31, 2014  
Presumptive Positives

Total = 14

Flow **concerning** for SCID

3 (21%)

**Jacobsen Syndrome**: [11Mb del 11q24.2q25] (CD3 = 1637)

1

- Gestational **diabetes**, polyhydramnios, concern for Trisomy 18
- Apneic/intubated at birth; congenital pneumonia; cytopenias; **NICU**
- Normal immune work-up; mild cytopenia at age 12 mon

**18p deletion/complex congenital heart disease** (CD3 = 651)

1

- Maternal anemia & hydronephrosis; **complex cong heart dz** (DORV)
- **Persistent chylothorax**, anasarca, pleural effusions; **NICU**
- *NBS drawn age >3 mon*
- NI immune work-up except for **persistent lymphopenia** at age 5 mon

Iowa SCID NBS Pilot June 3, 2013 – June 30, 2014 Presumptive Positives	Total = 14
Flow <b>concerning</b> for SCID	3 (21%)
<p><b>Jacobsen Syndrome:</b> [11Mb del 11q24.2q25] (CD3 = 1637)</p> <ul style="list-style-type: none"> <li>- Gestational <b>diabetes</b>, polyhydramnios, concern for Trisomy 18</li> <li>- Apneic/intubated at birth; congenital pneumonia; cytopenias; <b>NICU</b></li> <li>- Normal immune work-up; mild cytopenia at age 12 mon</li> </ul>	1
<p><b>18p deletion/complex congenital heart disease</b> (CD3 = 651)</p> <ul style="list-style-type: none"> <li>- Maternal anemia &amp; hydronephrosis; <b>complex cong heart dz</b> (DORV)</li> <li>- <b>Persistent chylothorax</b>, anasarca, pleural effusions; <b>NICU</b></li> <li>- <i>NBS drawn age &gt;3 mon</i></li> <li>- NI immune work-up except for <b>persistent lymphopenia</b> at age 5 mon</li> </ul>	1
<p><b>T cell lymphopenia – unexplained</b> (CD3 = 286)</p> <ul style="list-style-type: none"> <li>- <b>Hosp</b> for fever on day of 2<sup>nd</sup> tier testing; <b>NICU</b>- seizure; <b>hypo-parathyroidism</b></li> <li>- Normal FISH, B+ SCID mutation panel, aCGH, WES</li> <li>- Normal immune work-up except for <b>persistent lymphopenia</b> (age 12 mon: CD3 = 586; age 24 mon: CD3 = 601)</li> </ul>	1

# Current data post pilot

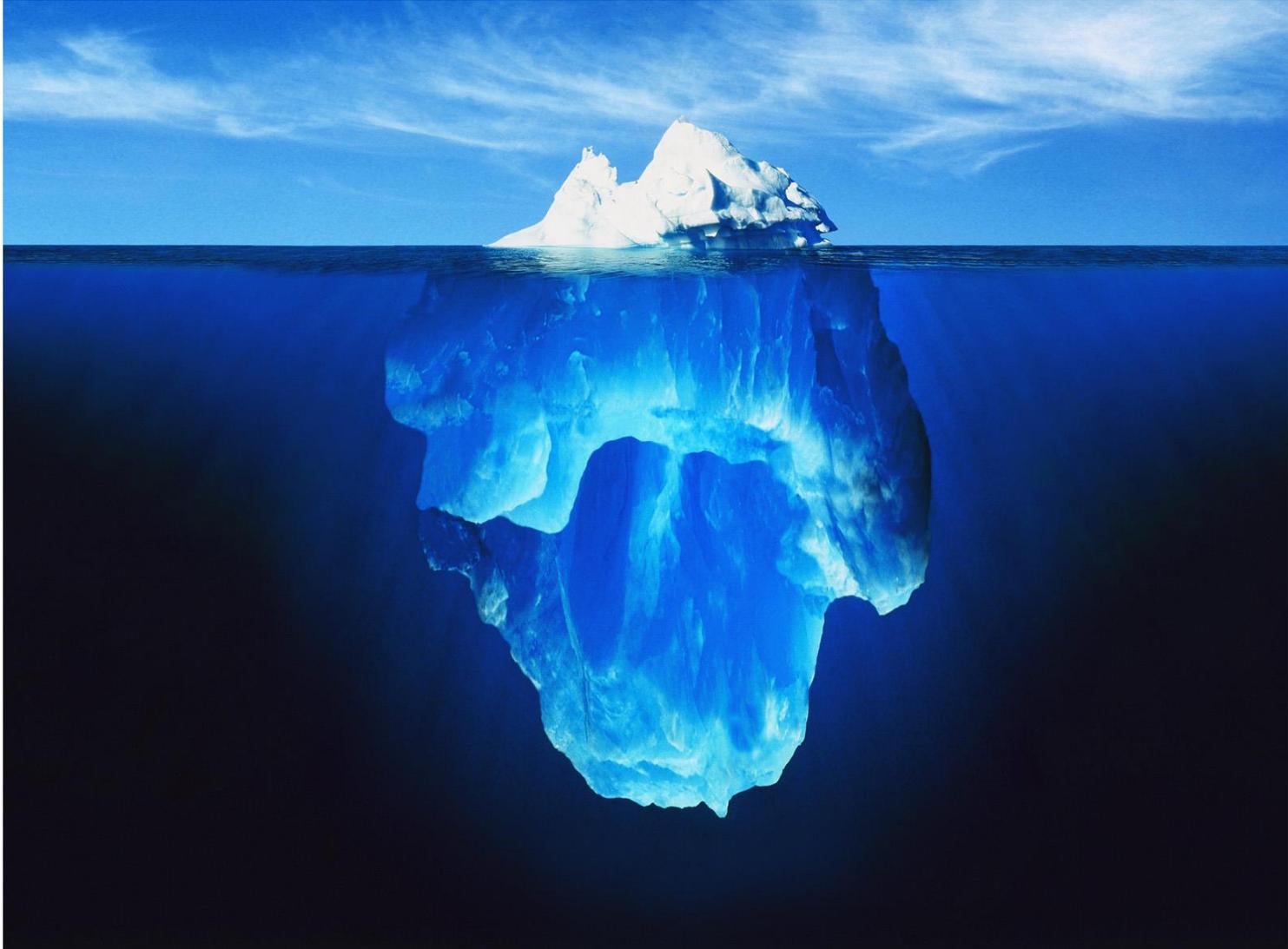
- July 2014 – April 2016
  - 20 presumptive positives
    - 2 with normal repeat NBS
    - 10 with normal flow
    - 1 declined 2<sup>nd</sup> tier testing
    - 7 with abnormal flow
      - 2 with resolution of T-cell lymphopenia; normal T-cell function
      - 3 with **22q11** deletion syndrome; normal T-cell function
      - 1 with **Trisomy 21**; normal T-cell function
      - 1 with persistent neutropenia; now normal CD3; normal T-cell function. **RASSF9** mutation of unclear significance

Iowa SCID NBS July 1, 2014 – April 29, 2016	Total
Presumptive Positive	20
Female	11/20 (55%)
Intensive care unit	9/20 (45%)
Congenital heart disease	6/20 (30%)
Infant of diabetic mother	4/20 (20%)
C-section	4/20 (20%)
Prematurity	4/20 (20%)
<i>Other</i> <ul style="list-style-type: none"> <li data-bbox="79 975 1431 1025">- Metabolic disorder</li> <li data-bbox="79 1039 1431 1089">- Possible fetal alcohol syndrome</li> <li data-bbox="79 1103 1431 1153">- Maternal thymic B-cell lymphoma; on chemo</li> <li data-bbox="79 1168 1431 1218">- Maternal HIV on HAART</li> </ul>	 2 1 1 1

Forms of Non-SCID Detected During Screening	CA	NY	LA	PR	WI	MA	Total
DiGeorge	5	3	0	2	2	4	16
Trisomy 21	1	1	0	0	0	0	2
CHARGE syndrome	0	1	0	0	0	0	1
T cell lymphopenia	2	7	0	5	3	2	19
Jacobsen Syndrome	0	0	1	0	0	1	2
Surgery/Other	0	0	3	0	3	2	8
Trisomy 18	0	1	0	0	0	0	1
6p deletion	0	1	0	0	0	0	1
B cell deficiency	0	4	0	0	0	0	4
Bare lymphocyte syndrome	0	1	0	0	0	0	1

–Newborn Screening Translational Research Group at  
<https://www.nbstrn.org/resources/scid-resources>

# SCID Newborn Screening Program – Iowa and elsewhere



# SCID Newborn Screening Group

- **University of Iowa Hospitals and Clinics**
- Dr. Mary Beth Fasano, Medical Consultant, SCID
- Dr. Polly Ferguson, Medical Consultant, SCID
- Dr. Sergei Syrbu, Medical Consultant, SCID
- Emily Phillips, SCID Newborn Screening Case Manager
- Carol Johnson, Iowa Newborn Screening Coordinator
- Courtney Kremer, SCID Long Term Follow Up
- Steve Rumelhart, SCID Long Term Follow Up
- **State Hygienic Laboratory**
- Newborn Screening
- Stan Berberich, PhD, Program Manager, Iowa Newborn Screening Laboratory
- Elizabeth McDonald, Clinical Laboratory Analyst
- Mike Ramirez, Supervisor, Iowa Newborn Screening Laboratory
- Valerie Van Zee, Clinical Laboratory Analyst
- Molecular Diagnostics
- Jing Bai, Clinical Laboratory Analyst
- Jeff Benfer, Supervisor, Virology and Molecular Biology
- Lucy DesJardin, PhD, Program Manager, Molecular Research and Development
- Travis Henry, PhD, Clinical Laboratory Analyst
- Trisha Kreman, Clinical Laboratory Analyst