

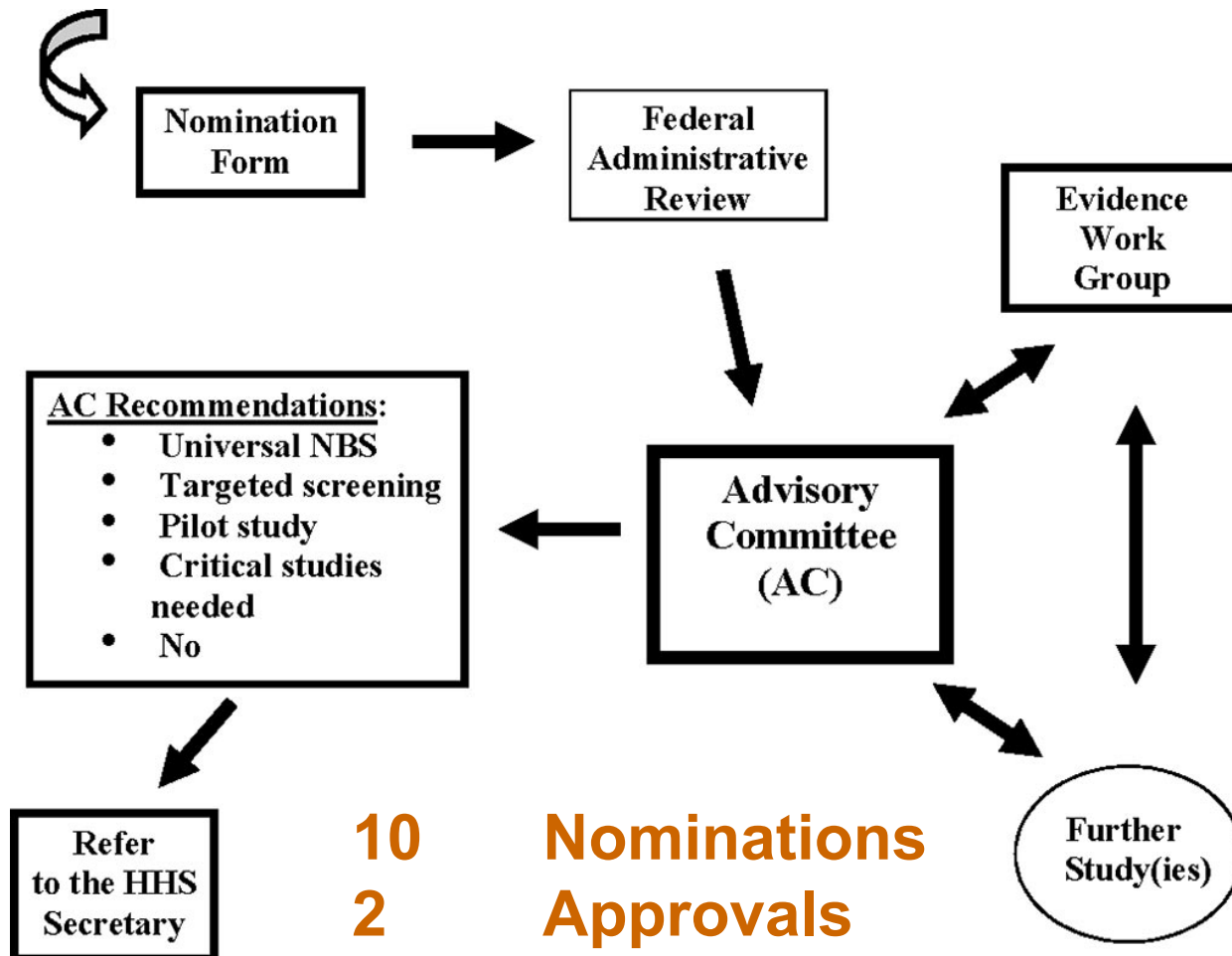
Translational Research in Newborn Screening: Efforts to Facilitate Implementation of Newborn Screening for Severe Combined Immune Deficiency (SCID)

**Michele Caggana, ScD presenting
for Amy Brower, PhD and Fred
Lorey, PhD
May 8, 2013**



Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC)

Nomination and Evidence Review Process



Key Events in Newborn Screening for SCID



(1971-1984)



American College of Medical Genetics **ACT SHEET**

Using ACT Sheet for
Screening for Severe Combined Immunodeficiency (SCID) and Conditions
Associated with T Cell Lymphopenia

Severe Combined Immunodeficiency (SCID) includes a group of rare but serious, and potentially fatal, conditions in which T lymphocytes fail to develop and B lymphocytes are either absent or compromised. The term "combined" leads to the term "combined." Untreated patients develop life-threatening infections due to the screening test for T cell receptor excision circles (TRECs), a byproduct of normal T cell development as well as certain related conditions with low T cells. For example DiGeorge Syndrome with low T cells and low TRECs.

FOLLOWING ACTIONS:

Inform them of the newborn screening result. Point out that additional tests are required to



- ◆ **Recommendation to add SCID in January 2010 and endorsed by HHS Secretary in May 2010**
- ◆ **Outlined the following activities**
 - **Education and Training Materials - The Health Resources and Services Administration [HRSA]**
 - **Quality Assurance - The Centers for Disease Control and Prevention [CDC]**
 - **Expanded Pilots - The National Institutes of Health [NIH]**

Key Components of Pilot

Pilot in High
Number Birth
States

High Capacity
Assay
Development

Regionalization
Model

CDC Quality
Assurance
Program

SCID R4S
Data Portal

NBSTRN
Administrative
Core



Expansion of SCID Newborn Screening Pilots

- ◆ **NICHHD initiated project to enable increased pilot screening**
 - contract to NYS held by K. Pass, PhD extended
- ◆ **Key Features**
 - Initiates pilots in high number birth states (New York, California)
 - High capacity assay development (New York, California)
 - Regionalization model
 - Puerto Rico → Massachusetts
 - Louisiana → Wisconsin
 - CDC quality assurance program
 - Utilize NBSTRN
 - SCID data portal – analytical validation
 - Long-term Follow-Up
 - Monthly conference calls to share expertise

Networks

- Clinical specialists
- State laboratories
- Federal partners
- Advocates and patients

Informatics

- Laboratory Performance Tool (R4S)
- Virtual Repository of Dried Blood Spots (VRDBS)
- Longitudinal Pediatric Data Resource (LPDR)

Infrastructure

Facilitate Research

- Natural history studies
- Novel screening technologies
- Novel therapies
- Genomics

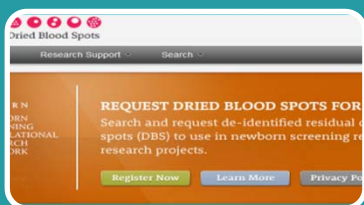
Focus

- Ethical, legal and social issues
- Study planning
- Data aggregation and discovery
- Statistics



R4S

- Analytical and clinical validation
- Laboratory protocols, definitions



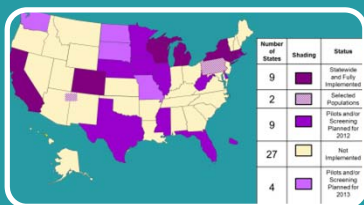
VRDBS

- Search and request de-identified residual dried blood spots
- Secure research support and request management



LPDR

- Secure, standards-based clinical data collection and management
- Aggregate, share, and analyze data



Stakeholder Engagement

- Facilitate communication between experts and key stakeholders
- Monthly conference calls



Disseminate Pilot Findings

SCID Resources

Statement of Work for National SCID Pilot Study

Frequently Asked Questions: Newborn Screening for Severe Combined Immunodeficiency (SCID) Information for Parents

What is newborn screening?

Every state has a newborn screening program to identify infants with rare disorders, which would not usually be detected at birth. Early diagnosis and treatment of these disorders often prevents serious complications.

What is severe combined immunodeficiency?

SCID is one of over 40 disorders included in newborn screening in New York State. It is a rare genetic disorder. Children with SCID have an immune system that does not work well. The immune system's job in the body is to fight off infections. Therefore, children with SCID have an increased risk to develop serious infections. There are usually no clues at birth that a baby has SCID.

How does New York State screen for SCID?

T cell receptor excision circles (TRECc) are usually found in every newborn's blood. As part of the NYS newborn screen, a specialist measures the amount of TRECc in each baby's blood. TRECc are made by T cells, which are an important part of the immune system. Babies with SCID have little to no TRECc in their blood.

My baby had a positive newborn screen for SCID. Does my baby definitely have SCID?

A positive newborn screen does not mean that your baby definitely has SCID. However, it means that additional blood tests are needed. Low levels of TRECc in the blood can be caused by SCID, prematurity or other, less serious immune disorders. It is also possible for a baby to have a positive newborn screen for SCID, but have a normal immune system.

How do I find out if my baby has SCID?

Your doctor will ask you to take your baby to see a special doctor, called an immunologist or an infectious disease specialist because they are experts at diagnosing and treating SCID. Additional blood tests will be ordered by the specialist to find out if your baby has SCID. The additional tests are very important. If diagnosis and treatment for SCID are delayed, it can lead to serious infections. In some cases, these infections are life threatening.

What is the treatment for SCID?

Children with SCID are treated with a bone marrow transplant.

No one else in my family has SCID or immune system problems.

Is it still possible for my baby to have the condition?

Even if no one in your family has SCID, it is possible for your baby to have the condition. In fact, most babies who have SCID do not have a family history of the disorder. If your baby is diagnosed with SCID, your doctor may suggest genetic counseling to discuss the chance for your future children to have SCID.

Who can I call if I have additional questions about newborn screening for SCID?

Your baby's doctor or the NYS Newborn Screening Program are resources for additional questions about newborn screening for SCID.

Newborn Screening Program staff can be contacted at
518-473-7552, Monday through Friday, 8 am until 5 pm.

Laboratory
SOPs

Analytical
Validation
Details

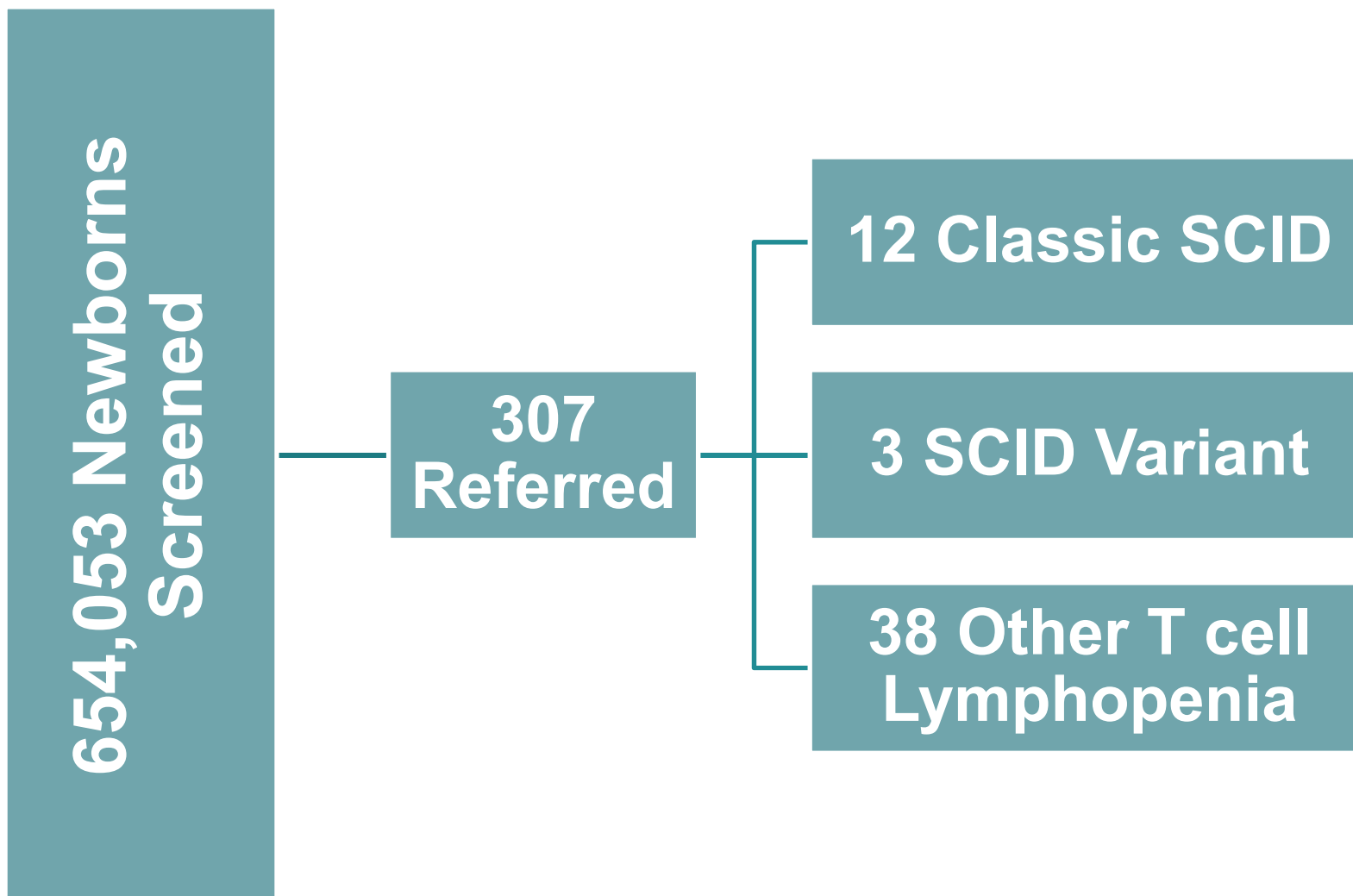
Technology
Elements

NY and CA
Laboratory
Algorithms

NY and CA
Clinical
Algorithms

CA and NY
Educational
Materials for
Families

CA, LA and NY
Educational
Materials for
Providers





Continued Efforts to Facilitate Implementation of SCID NBS

- ◆ **Disseminate Pilot Findings and Resources**
 - Statement of Work for National SCID Pilot Study
 - Protocols and Algorithms
 - Support the R4S SCID Data Portal
- ◆ **Newer and Continuing Efforts**
 - Monthly Stakeholder Calls
 - Expansion of R4S SCID Data Portal (e.g. participants and capability)
 - Longitudinal Data Collection
 - Inclusion of Families and Advocacy Groups
 - Work with PIDTC and Other Partners

SCID Resources

- Immune Deficiency Foundation Parent Brochure on SCID Customizable brochure for positive n screen.
- SCID Parents Guide for Positive Diagnosis

Newborn Screening for Severe Combined Immunodeficiency and Conditions Associated with T Cell Lymphopenia

Babies can look healthy at birth and still have health problems that need to be recognized and treated. For your baby, fast routine newborn screening tests done in the hospital before discharge. A few days after birth, your baby's heel and tested for a number of disorders. One of the tests performed is to detect if the immune system. Your baby had a mark on this test that was either abnormal or did not give a clear. Additional testing needs to be done as soon as possible.

Severe Combined Immune Deficiency (SCID)

What Does An Abnormal Screening Test Mean?

The screening test shows that your baby may have a low number of a type of white blood cells called "T cells." Low numbers of T cells can be associated with a genetic condition called Severe Combined Immunodeficiency or SCID (pronounced "skid") which would place your baby at extreme risk for serious, life-threatening infections. The screening test alone cannot be used to make a diagnosis of SCID, which is why a new blood test is needed to determine if your baby has a life-threatening immune disorder. You will receive instructions from your medical provider or your state newborn screening program about getting a new specimen without delay.



What is SCID?

SCID is a set of more than a dozen different genetic disorders, all of which result in a failure to develop T cells and to make protective antibodies. Most newborns with SCID appear healthy at first because the mother's immune system protects them from infections for the first few weeks of life. However, without treatment, even common infections can be life-threatening. If your baby has SCID a treatment plan can be started to help prevent infections and establish a functioning immune system.

What Other Immune System Problems Could My Baby Have?

In addition to SCID, the screening test also picks up other conditions associated with low T cells. These are often referred to as SCID, but are important to find out about and treat. Although these are immune disorders they are not HIV or AIDS and are not infectious.

How Common is SCID?

In past years, it was believed that the incidence for babies born each year with SCID was 1 in 100,000. New data from states that have instituted newborn screening programs for SCID suggest that the incidence may be somewhat common.

How are SCID and Other Conditions Associated with T cell Lymphopenia Treated?

The most effective treatment for SCID is a bone marrow transplant. This treatment can be done soon after birth with high success rate when done in the first few months of life. Some of the other conditions associated with low T cells can be treated with bone marrow transplant, while others may be most appropriately treated with or without hematopoietic stem cell transplantation. An immunologist will determine what kind of treatment your baby needs.



A Guide for Parents Following a Diagnosis

Disseminate Resources Developed by Additional States

SCID Resources

Massachusetts State Newborn Screening Program Brochures:

- [Newborn Screening in Massachusetts: Answers for You and Your Baby](#)

Wisconsin State Newborn Screening Program Brochures:

- [Just a Few Drops of Blood...Can Detect Serious Hidden Disorders in Your Baby](#)



COMMONWEALTH OF MASSACHUSETTS

Commonwealth Medicine

Just A Few Drops Of Blood... Can Detect Serious Hidden Disorders In Your Baby

What is newborn screening?
Newborn screening is a special blood test for newborns. Just a few drops of blood from your baby's heel are put onto a special test paper and sent to the Wisconsin State Lab of Hygiene to be tested. Newborn screening finds babies who may have a hidden disorder that needs early treatment.

Is the test safe?
The test is simple and safe. Some babies cry when their heel is pricked, but the discomfort lasts only a short time. The risk of infection when the heel is pricked. This risk is very low.

What are "hidden" disorders?
Hidden disorders are health problems that are difficult or impossible for you or your baby's doctor to find just by looking at your baby. If not treated, these disorders can lead to slow growth, severe illness, brain damage, or possibly death. Early treatment can help prevent some of these serious health problems.

How will I know the results of my baby's screening test?
Your baby's doctor will receive a report with the test result about these results when you take your baby in for a regular check-up.

Why must my baby be screened?
Wisconsin law requires that all babies born in Wisconsin be screened before leaving the hospital. If your baby is born outside of a hospital, the screening test must be done within a week of birth.

What if my baby's test is abnormal?
If the test is abnormal you will be contacted within a few days after you leave the hospital. If your baby's newborn screening result is abnormal, your doctor will talk with you about the steps to take. An abnormal newborn screening result does mean that your baby has a disorder. This is a screening test that finds babies who may be at risk for a disorder. Further testing must be done to find out if your baby has a disorder and if treatment is needed.

Can I say "no" to the test?
As a parent, you may refuse newborn screening for your baby only if your religious beliefs and practices do not allow this testing. If you refuse to have the test done, you may be asked to sign a paper stating that you refused to have your baby tested for these very serious disorders.

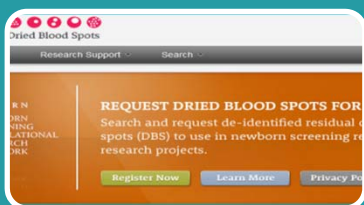
Why do some babies need to be retested?
There are two main reasons why a repeat screening test is needed: (1) there was a problem with the way the first blood sample was collected, or (2) the test result was abnormal. If you have a repeat screening test, a new blood sample is taken from your baby. The newborn screening test is most accurate when your baby's blood is taken after the first 24 hours of life. If

Available in other languages:
<http://www.massmed.edu/nbs/>



R4S

- Analytical and clinical validation
- Laboratory protocols, definitions



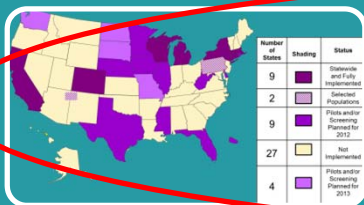
VRDBS

- Search and request de-identified residual dried blood spots
- Secure research support and request management



LPDR

- Secure, standards-based clinical data collection and management
- Aggregate, share, and analyze data

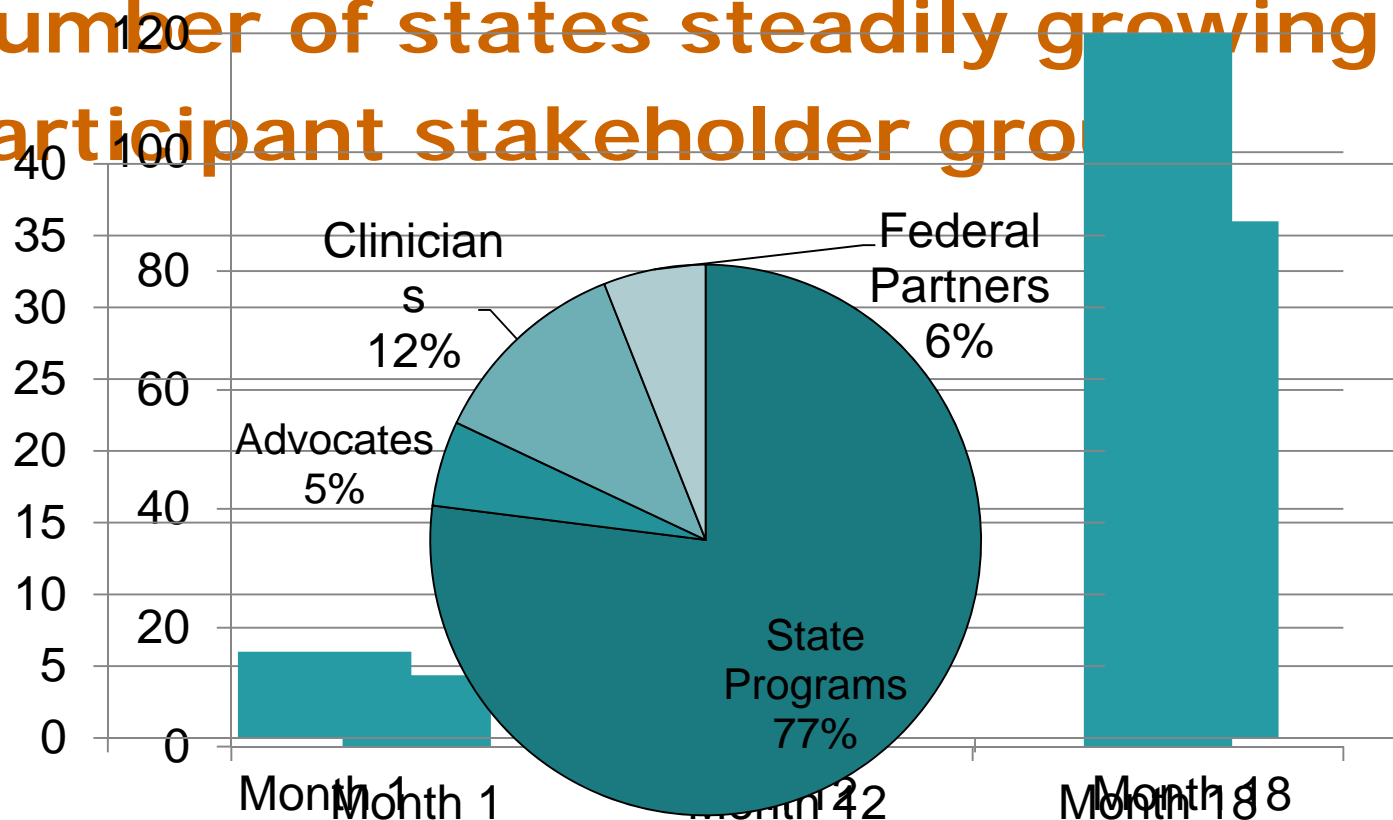


Stakeholder Engagement

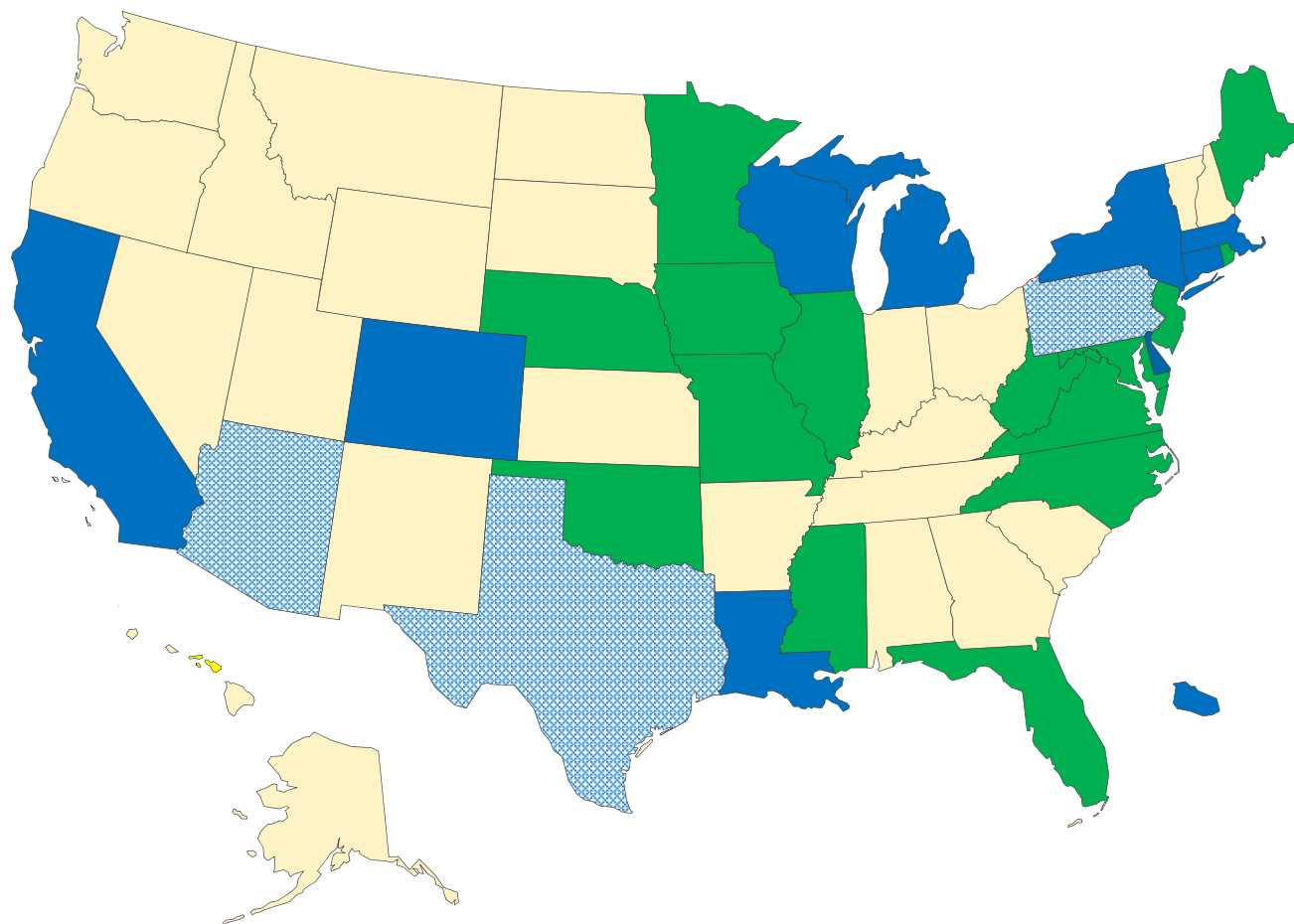
- Facilitate communication between experts and key stakeholders
- Monthly conference calls





- ◆ **Sample Standing Agenda**
 - Introduction of New Participants
 - Implementation Status Review and Stakeholder Reports
 - Effort to Report on National Experience
 - CDC Update
 - IDF Meeting
 - Resources and Tools
 - Submitted Discussion Items
 - Discussion

- ◆ **Number of participants steadily growing**
- ◆ **Number of states steadily growing**
- ◆ **Participant stakeholder growth**

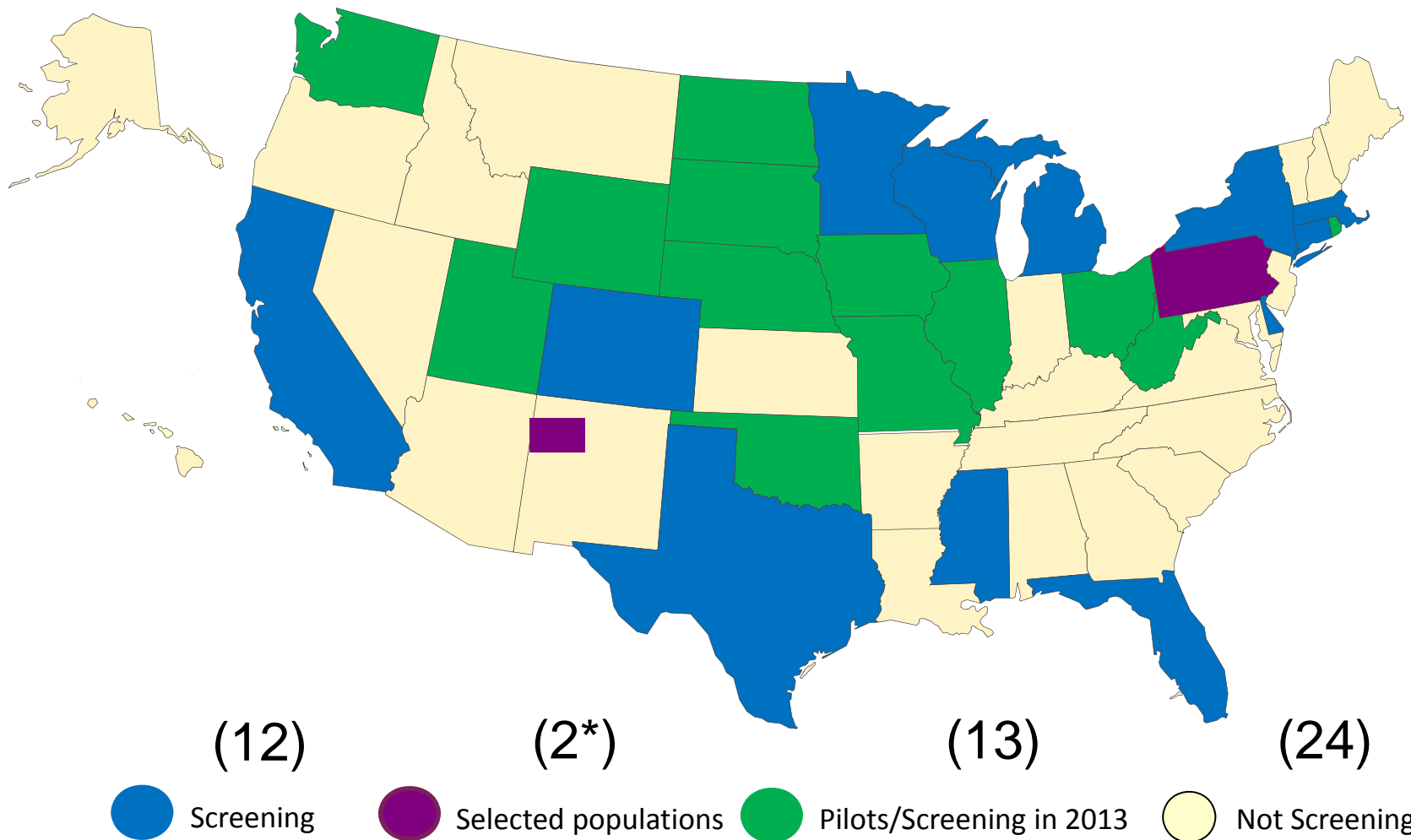


January 2012 Update



Number of States	Shading	Status
10		State-wide Screening
3		Partial Screening
16		Screening approved
22		Fact Finding

March 2013 Implementation Status



Selected Stats

Total
Number of
Newborns
Screened
by
12/31/12

Percentage
of Births
Screened

States
Planning
Pilots or
Screening
in 2013

Estimated
Percentage
of Births
Screened
by 2014

Clinically
Diagnosed
Cases
Since RUSP
Addition in
Non-
screening
States

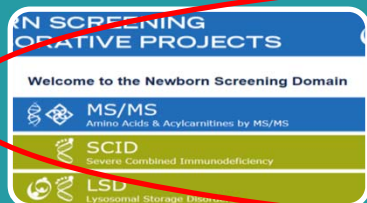
2.85 M

45%

13

62%

15+ +



R4S

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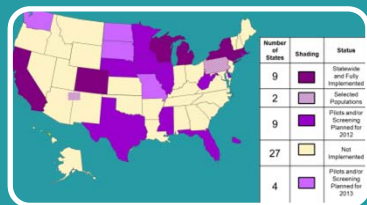
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NEWBORN SCREENING COLLABORATIVE PROJECTS



Welcome to the Newborn Screening Domain

-  **MS/MS**
Amino Acids & Acylcarnitines by MS/MS
-  **CAH**
Congenital Adrenal Hyperplasia
- BIOT**
Biotinidase Deficiency
- MS/MS [2]**
Amino Acids & Acylcarnitines by MS/MS [2nd Sample]
- CH**
Congenital Hypothyroidism
-  **SCID**
Severe Combined Immunodeficiency
-  **LSD**
Lysosomal Storage Disorders
-  **ALD**
Adrenoleukodystrophy
-  **FRDA**
Friedreich Ataxia
-  **WD**
Wilson Disease

- Co-curators
 - Roshini Abraham, PhD
 - Fred Lorey, PhD

SCID COLLABORATIVE PROJECT



Home Data Submission Tools & Reports User Settings Documentation Site Admin Log Out

Welcome: Amy M Brower

True Positive Outliers

Analyte Type: Demographics
 TCR excision circle
 Control
 Confirmatory testing

Analyte: **- Selection -**
 - Selection -
 BW (g)
 GA (wks)
 Coll age (days)
 Coll weight (g)

Analyte Type: Demographics
 TCR excision circle
 Control
 Confirmatory testing

Analyte: **- Selection -**
 - Selection -
 RNaseP
 β-actin

Analyte Type: Demographics
 TCR excision circle
 Control
 Confirmatory testing

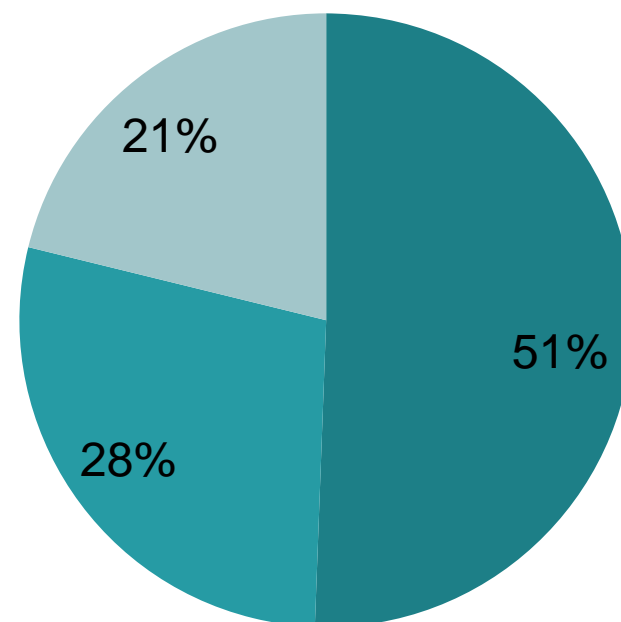
Analyte: **Lymphocytes**
 - Selection -
 Hb
 Platelets
 WBC
 Neutrophils
Lymphocytes
 Monocytes
 Eosinophils
 CD45-flow
 CD3 T cells-flow
 CD4 T cells-flow
 CD8 T cells-flow
 CD19 B cells- flow
 NK cells-flow
 CD4 naive T cells
 CD4 memory T cells
 CD8 naive T cells

CaseID	Condition	Participant
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◆ 86 Registered Users

- States Screening
- States Planning Screening
- International Groups
- NBSTRN
- NICHD
- APHL
- CDC
- Mayo



■ Screening States ■ Planning States ■ Other

Definitions Used in R4S, PIDTC and CLSI Document

Category	Name	Details
1	Typical SCID	<300 autologous T cells/u; Emergent Rx – HCT, enzyme or gene therapy
2	Leaky SCID/Omenn Syndrome	300-1500 autologous T cells at lower limit; Require HCT, enzyme or gene therapy
3	Variant SCID	Usually 300-1500 autologous T cells; May or may not require HCT
4	Syndromes with T Cell Impairment	<1500 CD3 T cells/uL; Some require HCT or thymus Tx
5	Secondary T Cell Lymphopenia Excluding Preterm Infants Alone	<=1500 CD3 T cells/uL; Includes conditions which cause non-intrinsic numerical T cell decrease
6	Preterm infants with T Cell Lymphopenia and No Other Recognizable Disorder	<=1500 CD3 T cells/uL

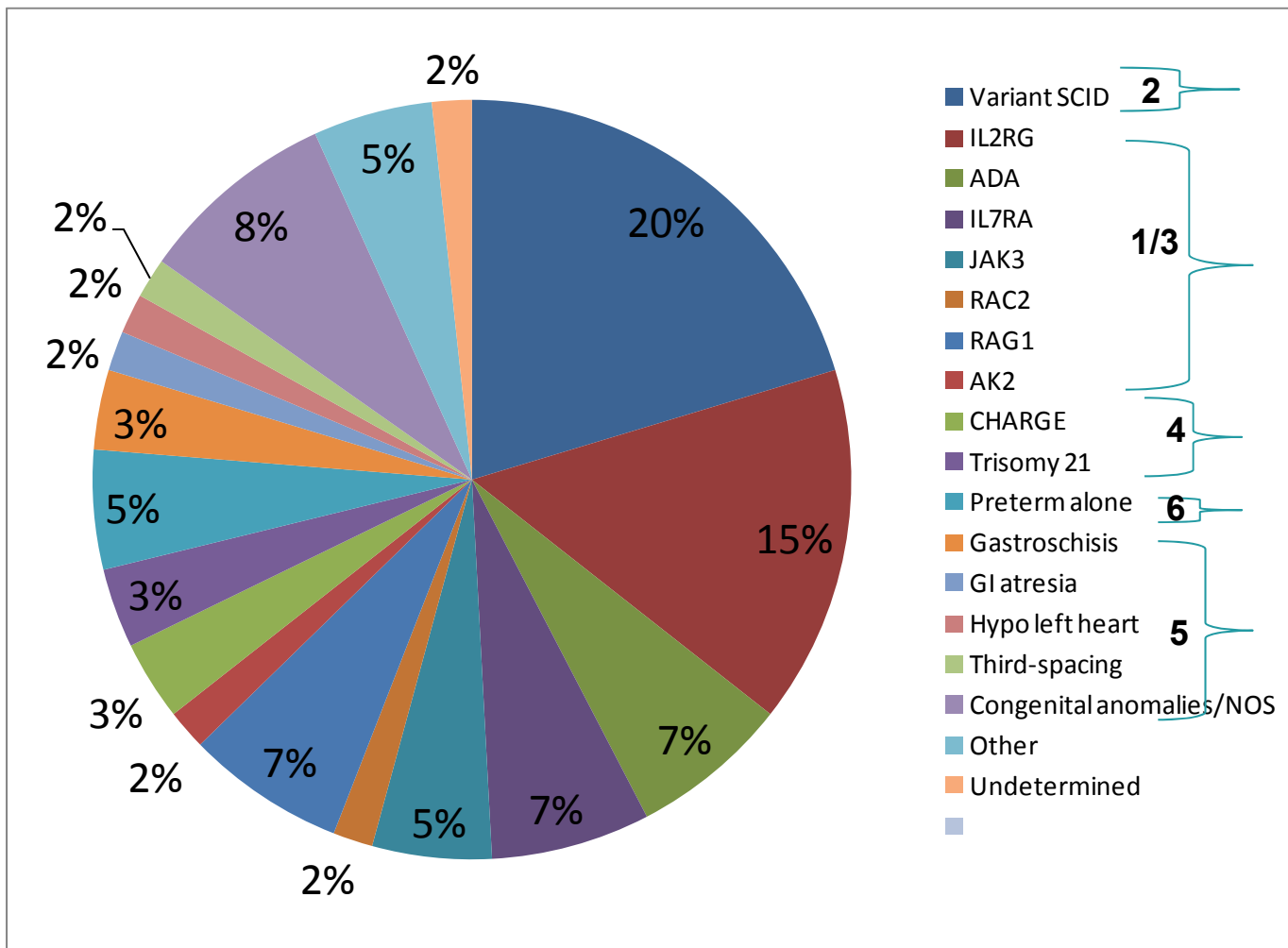
Distribution of True Positive Cases

77 Cases Classified

CA

NY

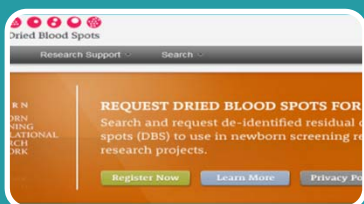
FL





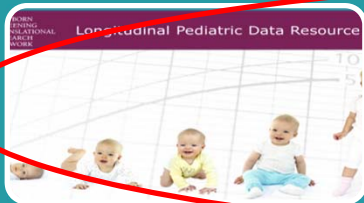
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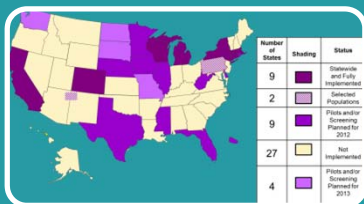
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Stakeholder Engagement

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Effort to Report on National Experience

- ◆ **Purpose – To report on the efforts and findings of the state-based newborn screening programs and the clinicians who diagnose and treat newborns identified with SCID and related T lymphocyte deficiencies.**
- ◆ **Scope – This report describes the screening, diagnosis and treatment activities of states that are actively screening for SCID. This is a descriptive report only and will not include statistical analysis of the submitted data.**

- **Continued Training Key Stakeholders in Use of SCID Module**
- **Utilization of SCID Module by All States and Programs**
- **Publish SCID National Pilot Findings**
- **Describe National Experience with SCID Newborn Screening**
- **Continue Monthly Calls to Engage and Inform Stakeholders**



Acknowledgments

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- Jennifer Puck, MD
- Robert Vogt, PhD
- Francis Lee, PhD
- Anne Marie Comeau, PhD
- Fred Lorey, PhD
- Mei Baker, MD
- Joanne Mei, PhD
- Carla Cuthbert, PhD

◆ **Tonight International B 8:30pm – 9:15pm**