Long-Term Follow-Up in Newborn Screening:

An Update on ACMG's Work on the NBSTRN and NCC

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Program Manager, NBSTRN and NCC

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American College of Medical Genetics and Genomics
Translating Genes Into Health®

Presentation Overview

- Background

- ACMG Coordinating Centers

- Current Efforts

- Case Studies
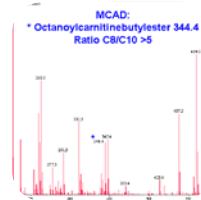
- Discussion

Goal of Newborn Screening

- Early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential

- Lifelong treatment in most cases

- Today's focus is on long-term follow-up

Prenatal Education

Screening

Diagnosis and Short-Term Follow-Up

Clinical Care and Long-Term Follow-Up

MCAD:
* Octanoylcarnitinebutylester 344.4
Ratio C8/C10 >5

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H.R. 1281 (113th): Newborn Screening Saves Lives Reauthorization of 2014

- Section 3: Extends through FY2019 a grant program to evaluate the effectiveness of screening, counseling, or health care services in reducing the morbidity and mortality caused by heritable disorders in newborns and children. Expands the program to include evaluation of health outcomes through adolescence and best practices for timely screening of newborns.

- Section 9: Authorizes the Secretary to expand the Hunter Kelly Newborn Screening Research Program to: (1) provide research and data for newborn conditions under review by the Advisory Committee to be added to the Recommended Uniform Screening Panel, and (2) conduct pilot studies on conditions recommended by the Advisory Committee to ensure that screenings are ready for nationwide implementation.

ONE HUNDRED THIRTEENTH CONGRESS OF THE UNITED STATES OF AMERICA

AT THE SECOND SESSION

Begun and held at the City of Washington on Friday, the third day of January, two thousand and fourteen

H. R. 1281

AN ACT

To amend the Public Health Service Act to reauthorize programs under part A of title XI of such Act.

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Advisory Committee on Heritable Disorders in Newborns and Children

- Provides guidance to reduce the morbidity and mortality associated with heritable disorders, with a special emphasis on those conditions detectable through newborn screening.

- Identified key features and defined the major overarching questions to be answered to assure newborn screening is meeting its goal of achieving the best quality outcome for the affected children an families.

Long-term follow-up after diagnosis resulting from newborn screening: Statement of the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Alex R. Kemper, MD, MPH[1], Coleen A. Boyle, PhD[2], Javier Aceves, MD[3], Denise Dougherty, PhD[4], James Figge, MD, MBA[5], Jill L. Fisch[6], Alan R. Hinman, MD, MPH[7], Carol L. Greene, MD[8], Christopher A. Kus, MD, MPH[9], Julie Miller, BS[10], Derek Robertson, MBA, JD[11], Brad Therrell, PhD[12], Michele Lloyd-Puryear, MD, PhD[13], Peter C. van Dyck, MD, MPH[13], and R. Rodney Howell, MD[14]

The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children provides guidance to reduce the morbidity and mortality associated with heritable disorders, with a special emphasis on those conditions detectable through newborn screening. Although long-term follow-up is necessary to maximize the benefit of diagnosis through newborn screening, such care is variable and inconsistent. To begin to improve long-term follow-up, the Advisory Committee has identified its key features, including the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of affected individuals. There are four components central to achieving long-term follow-up: care coordination through a medical home, evidence-based treatment, continuous quality improvement, and new knowledge discovery. *Genet Med* 2008:10(4):259–261.

Key Words: neonatal screening, comprehensive health care, guideline

What questions should newborn screening long-term follow-up be able to answer? A statement of the US Secretary for Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children

Cynthia F. Hinton, PhD, MPH[1], Lisa Feuchtbaum, DrPH, MPH[2], Christopher A. Kus, MD, MPH[3], Alex R. Kemper, MD, MPH[4], Susan A. Berry, MD[5], Jill Levy-Fisch, BA[6], Julie Luedtke, BS[7], Celia Kaye, MD, PhD[8], and Coleen A. Boyle, PhD, MS[1]

Abstract: The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children provides guidance on reducing the morbidity and mortality associated with heritable disorders detectable through newborn screening. Efforts to systematically evaluate health outcomes, beyond long-term survival, with a few exceptions, are just beginning. To facilitate these nascent efforts, the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children initiated a project to define the major overarching questions to nated effort to improve tracking and monitoring of healthcare delivery (e.g., services used, clinical care received, and health-related outcomes). Efforts to systematically evaluate health outcomes, beyond long-term survival, with a few exceptions, are just beginning. To facilitate these nascent efforts, the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) initiated a project to define the major overarching questions to

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Statement on Long-Term Follow-Up

Assure the best possible outcome for individuals with disorders identified through newborn screening

Key Features

Central Components

- Quality chronic disease management
- Condition-specific treatment
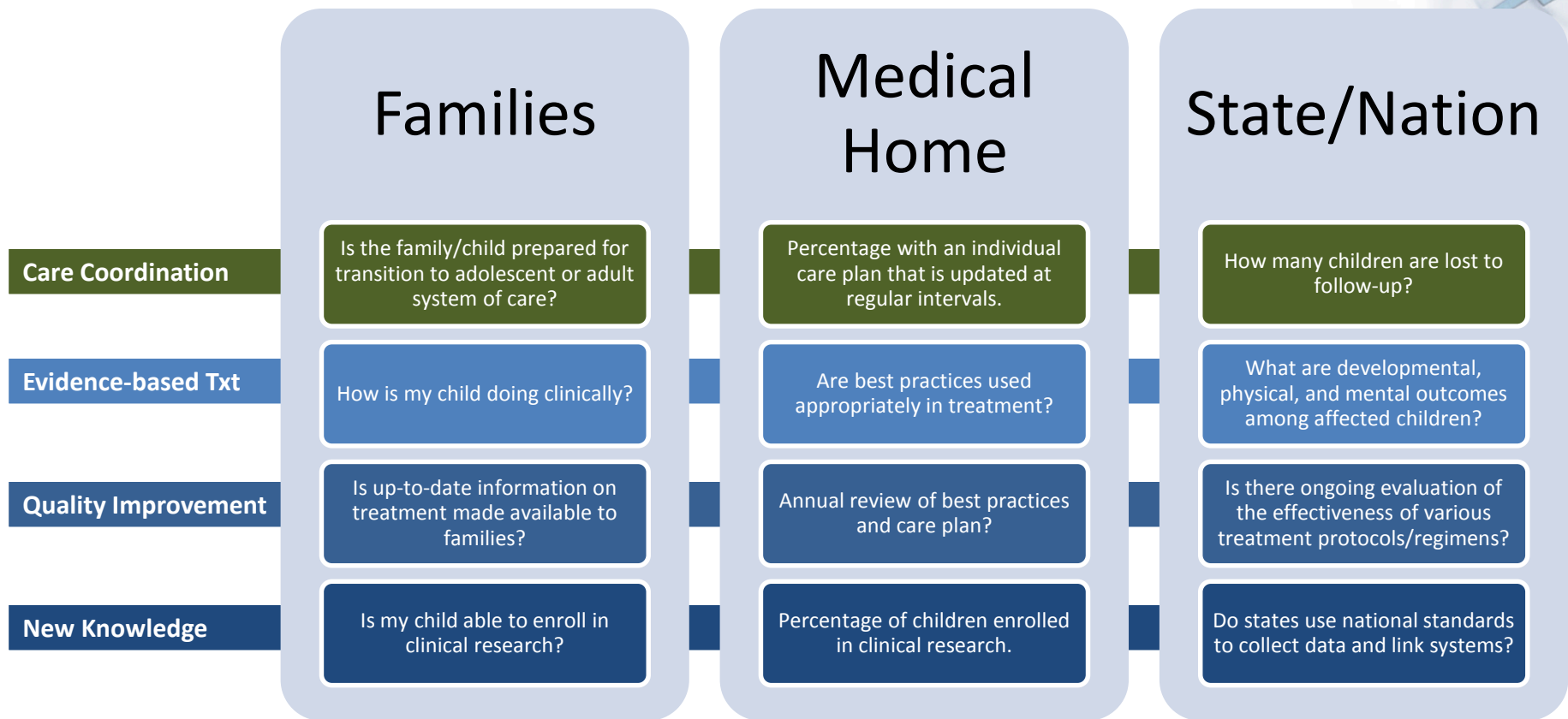- Age-appropriate preventive care throughout the lifespan
- Care coordination through a medical home
- Evidence-based treatment
- Continuous quality improvement
- New knowledge discovery

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Overarching Questions

	Families	**Medical Home**	**State/Nation**
Care Coordination	Is the family/child prepared for transition to adolescent or adult system of care?	Percentage with an individual care plan that is updated at regular intervals.	How many children are lost to follow-up?
Evidence-based Txt	How is my child doing clinically?	Are best practices used appropriately in treatment?	What are developmental, physical, and mental outcomes among affected children?
Quality Improvement	Is up-to-date information on treatment made available to families?	Annual review of best practices and care plan?	Is there ongoing evaluation of the effectiveness of various treatment protocols/regimens?
New Knowledge	Is my child able to enroll in clinical research?	Percentage of children enrolled in clinical research.	Do states use national standards to collect data and link systems?

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- **ACMG Coordinating Centers**
- Current Efforts
- Case Studies
- Discussion

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ACMG Coordinating Centers

NBSTRN
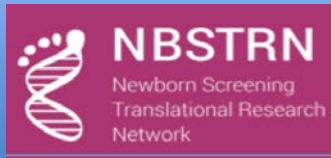
- NICHD Contract – Established 2009
- Current Funding 5 Years – Through 2018
- Improve the health outcomes of newborns with genetic or congenital disorders by means of an infrastructure that allows investigators access to robust resources for newborn screening research.
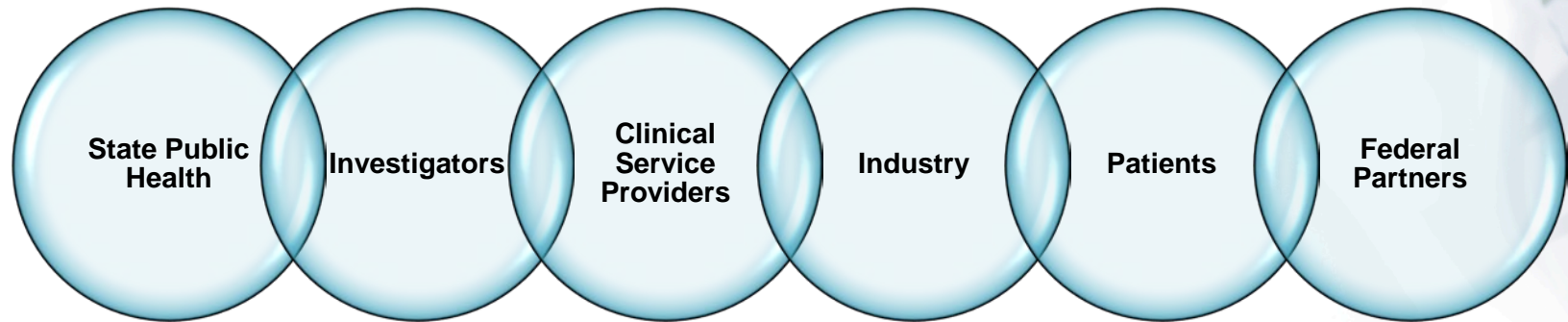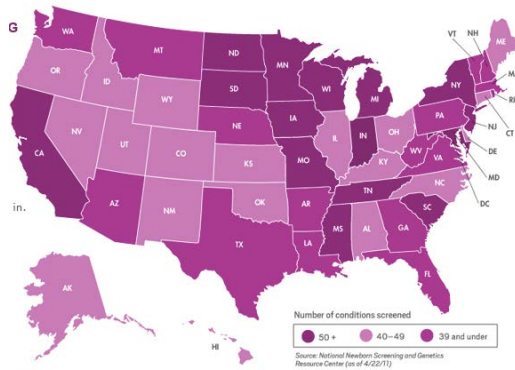
NCC

- HRSA – Established 2004
- Current Funding 2 Years – Through 2017
- Strengthen and support the genetics and newborn screening capacity of the states, to improve the availability, accessibility, and quality of genetic services and resources for individuals having, or at risk for, genetic conditions and their families across the lifespan.

Key Considerations in Newborn Screening

Bridging Between Diverse Stakeholders

State Public Health — Investigators — Clinical Service Providers — Industry — Patients — Federal Partners

Begins in State Public Health Newborn Screening Programs

Number of conditions screened
50+   40-49   39 and under
Source: National Newborn Screening and Genetics Resource Center (as of 4/22/11)

- Controlled through State Departments of Health
- Requires working with 50+ independent entities
- Chronic conditions requiring life-long medical care
- Care received in diverse settings
- Majority are rare or very rare
- Lack of natural history studies
- Incomplete understanding of genomic contributions

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Presentation Overview

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Development of LTFU Tools

Joint Committee
- Common Data Elements (CDEs)
- RUSP Conditions
- Subject Matter Experts
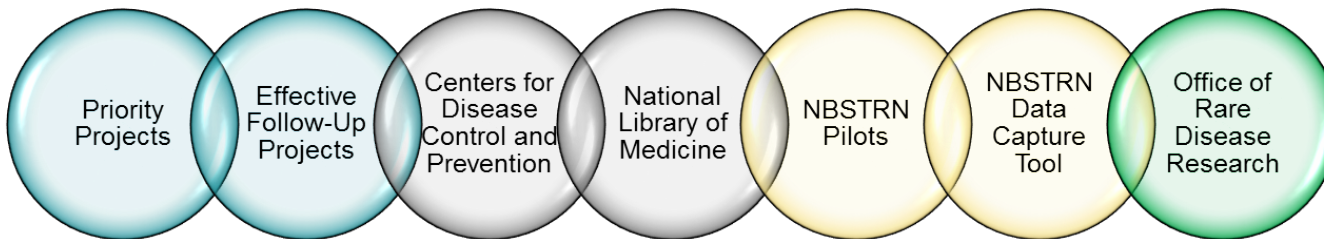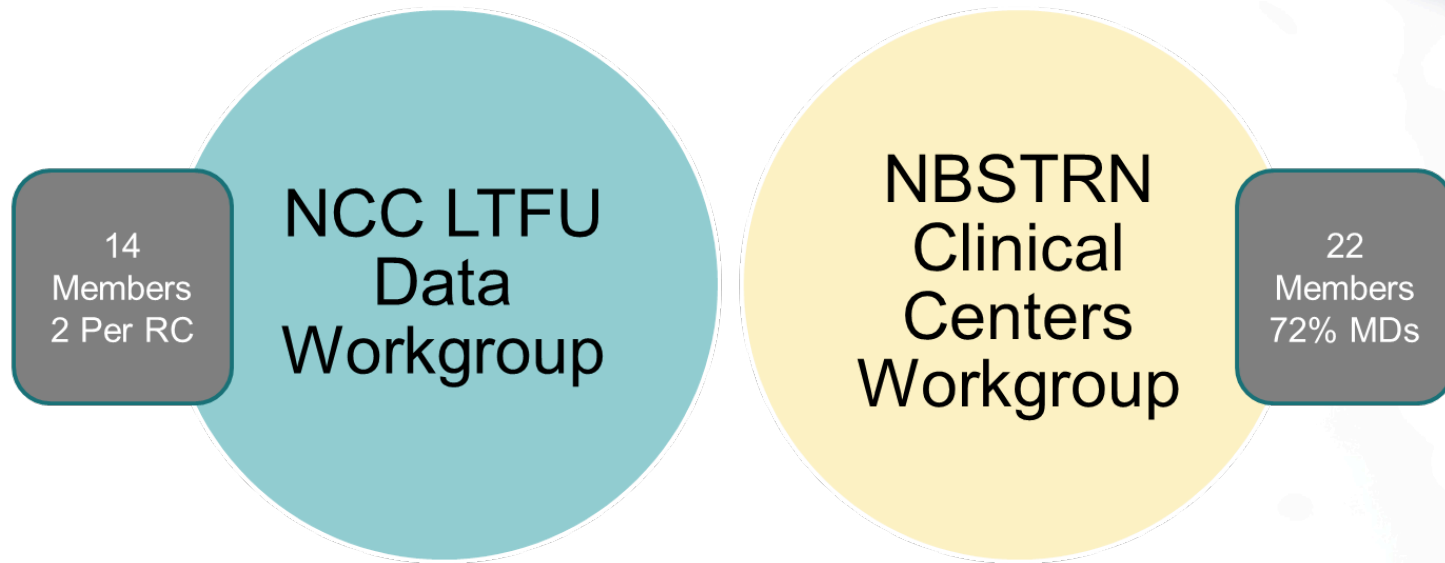- Applicable for Research and Public Health

NBSTRN
- Informatics Infrastructure
- Disease Specific and Candidate Conditions CDEs
- Clinical Integration Workgroup
- Pilots and Grantees

NCC
- Public Health Focus
- Leveraging the Regional Genetics Collaboratives
- NCC/RC LTFU Data Workgroup
- Pilots

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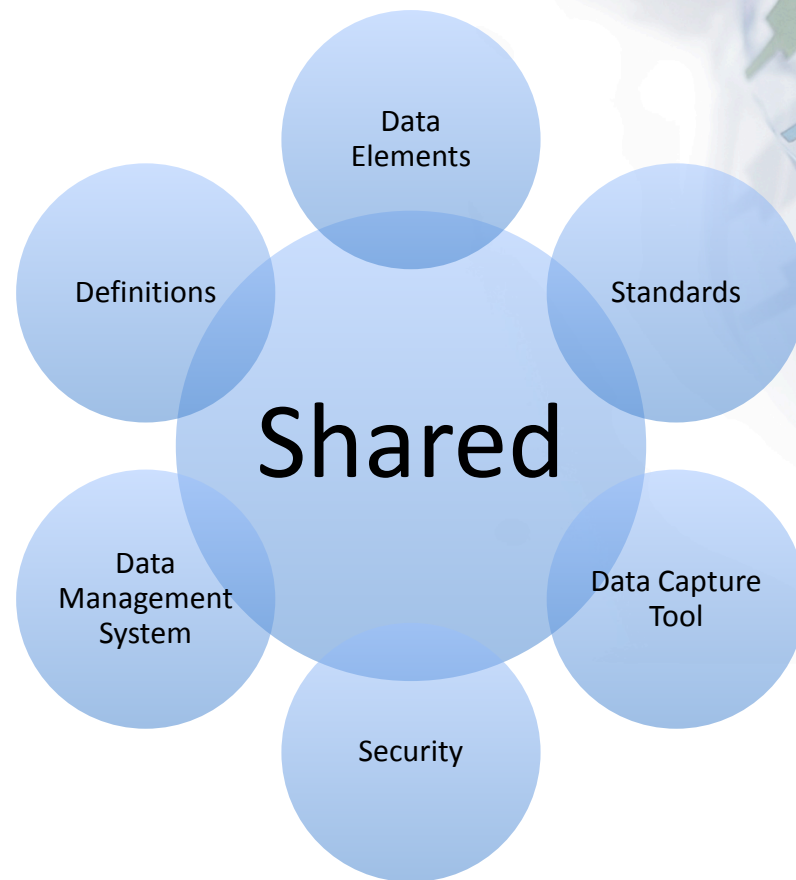- NCC/RC LTFU Data Workgroup
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Makeup of Joint Committee

14 Members 2 Per RC

NCC LTFU Data Workgroup

NBSTRN Clinical Centers Workgroup

22 Members 72% MDs

Priority Projects

Effective Follow-Up Projects

Centers for Disease Control and Prevention

National Library of Medicine

NBSTRN Pilots

NBSTRN Data Capture Tool

Office of Rare Disease Research

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Key Components

Objectives

- Enable investigators and public health teams to systematically collect, analyze and share data across the research community

Resource

- Information system using consensus standardized data sets, case report forms, secure data collection, sharing and management

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Potential Uses of Data Sets

National Data Set	Natural History
Research	Hypothesis Driven & Generating
Public Health	Surveillance, Outcomes, Quality Assurance & Improvement
NQF	Benchmarks

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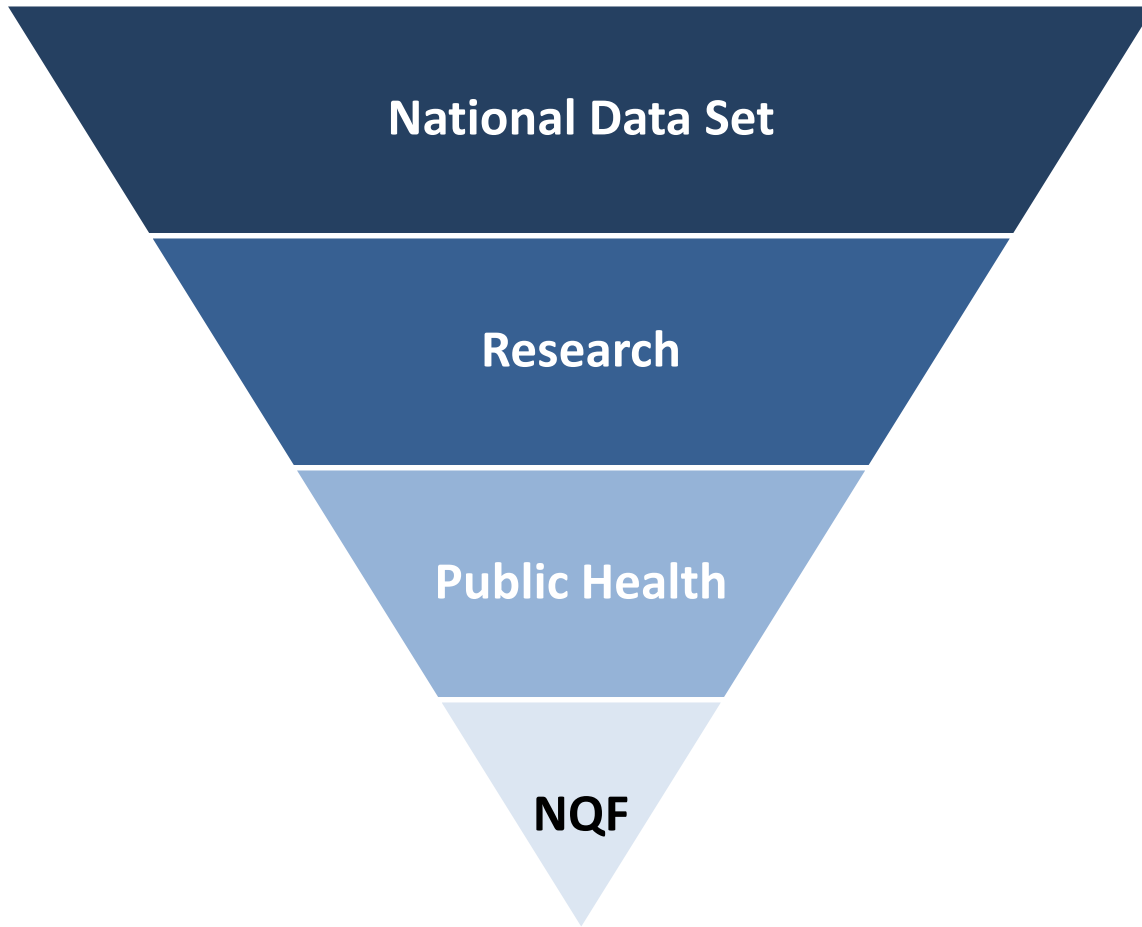
Use Cases

Investigator – New & Existing Technologies, Novel Treatment & Management Strategies

- Enable Novel Statistically Robust Proposals

Describe the clinical course of NBS identified conditions in which patients are asymptomatic.

Grantee – New & Existing Technologies, Novel Treatment & Management Strategies

- Accelerate & Facilitate Research

What is the relationship between CFTR genotypes and lung function in adolescence for newborn screen identified cystic fibrosis patients?

Public Health Partner – Service Delivery & Quality Assurance/Improvement

- Implement Technologies & Assess Health Outcomes for Novel Treatments

Describe the relationship between service delivery and treatment methods to define optimal follow-up care plans for children with MCAD.

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Scope of Work

32 Core
26 Secondary

New
Conditions

Recommended Uniform Panel (RUSP)

Evidence Review Process

Key Drivers

Long-Term Follow-Up Statement

Newborn Screening Saves Lives Act

4
Components

Management & Outcomes

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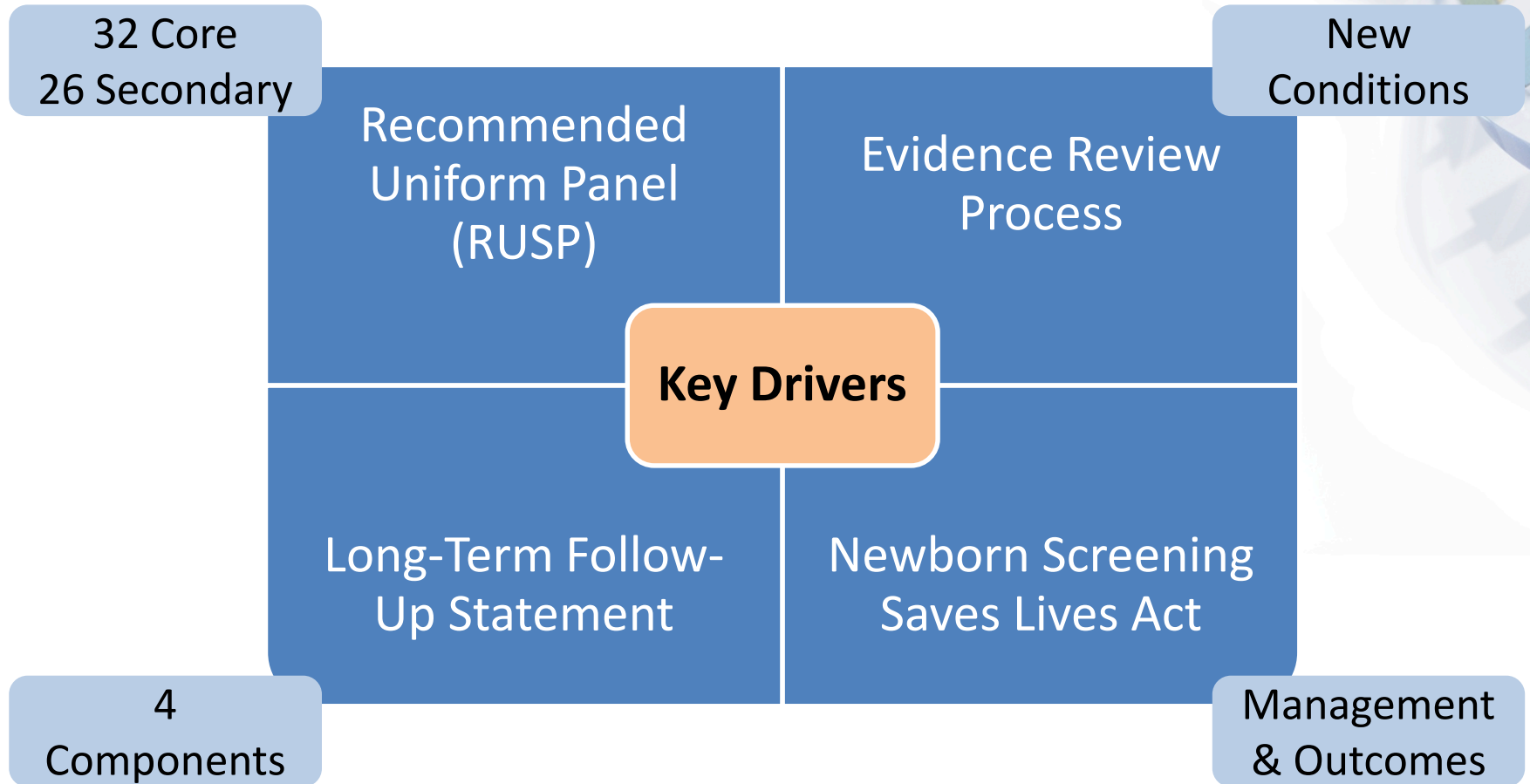
Common Data Elements (CDEs)

NBS Conditions

RUSP

Candidates

Development

Consensus

Grantee

Grantee

Consensus

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Current Efforts

Joint Committee	• Common Data Elements (CDEs) • RUSP Conditions • Subject Matter Experts • Applicable for Research and Public Health
NBSTRN	• Informatics Infrastructure • Disease Specific and Candidate Conditions CDEs • Clinical Integration Workgroup • Pilots and Grantees
NCC	• Public Health Focus • Leveraging the Regional Genetics Collaboratives • NCC/RC LTFU Data Workgroup • Pilots

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Facilitating Newborn Screening Research

- The NBSTRN is an NICHD funded contract awarded to ACMG (September 2013 - September 2018)

- The NBSTRN will develop, maintain, administer and enhance resources to support investigators with projects related to newborn screening for:
  - New technologies
  - New Conditions
  - New treatments and management approaches

NBSTRN
Newborn Screening
Translational Research
Network

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NBSTRN Tools

VRDBS

R4S

LPDR

ELSI

Advantage

- The **Virtual Repository of Dried Blood Spots (VRDBS)** is an open-source, web-based tool that enables NBS researchers to search over 2.9 million DBS from participating states.

- The **Region 4 Stork** tool is a web-based application for the collection and reporting of analytical results. It has been widely adopted into the routine practice of newborn screening laboratories worldwide.

- The **Longitudinal Pediatric Data Resource (LPDR)** is a secure informatics system designed to enable enhanced data collection, sharing, management and analysis for conditions identified as part of newborn screening or for conditions that may benefit from newborn screening.

- The **ELSI Advantage** is an ethical, legal and social issues resource for NBS researchers. Information on IRBs, NBS related FAQs and templates to customize your own consent forms.

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Longitudinal Pediatric Data Resource (LPDR) Mission

- The majority of NBS conditions are rare and translating new discoveries into clinical practice requires prospective collection, aggregation and sharing of health information

- To facilitate this translation the NBSTRN developed the Longitudinal Pediatric Data Resource which includes:
    - Data Sets
    - Data Almanac
    - Informatics System
    - Discovery Interface

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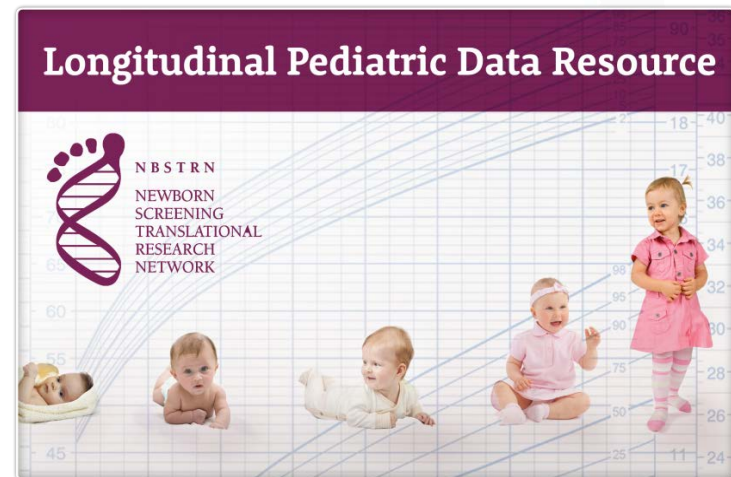
Welcome

The Longitudinal Pediatric Data Resource (LPDR) is a suite of information technology tools to support newborn screening researchers. The LPDR enables longitudinal collection of clinical and research information within a secure environment that provides permission-based access and data sharing to research teams. Leading clinicians and public health professionals have created a series of questions and answers organized into common data elements (CDEs) to capture important information about each of the conditions that are part of routine newborn screening, the Recommended Uniform Screening Panel (RUSP), or are candidates for newborn screening.

Learn More   Privacy Policy

Case Report Forms
Download disease specific PDFs containing common data elements

Data Almanac
Browse available common data elements

Integrate Genomics
Coming Soon!

REDCap™ Demo
Try out REDCap using sample forms

NBSTRN Support
Consult with staff and request a letter of support.

Request Level 2 Access
Apply for expanded use of the LPDR.

Plan Your Research   **Collect & Contribute**   **Query & Analyze**   **Report & Share**

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Current Conditions and Cohorts

Consensus N = 46	Draft N = 7	Development N = 12	Future N = 3+
14 RUSP AA	4 Hemoglobinopathies	SMA	Duchenne Muscular Dystrophy
15 RUSP OA	2 Endocrinopathies	7 LSDs	Krabbe
13 RUSP FA	Hearing Loss	NICU	Public Health
1 RUSP Biotinidase		Healthy Cohort	
3 RUSP Galactosemia		2 SCID	

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Current Consensus and Grantee CDEs

Total
10,216

| Metabolic 6136 | SMA 1637 | LSD 1201 | PCH 348 | NICU 405 to 836 | NSIGHT 1702 |

Intake

- Demographics
- Family History
- Newborn Screening
- Initial Testing
- Past Health History

Visit

- Demographics and Family History
- Health History
- Lab Studies
- Findings
- Management and Treatment – Nutrition
- Management and Treatment – Pharmacotherapy
- Other Studies

Other

- Study Status
- Pregnancy
- Dialysis
- Transplant

REDCap™ Case Report Forms

Subject | **Longitudinal Care Record**

- Intake • Visit • Study Status

2000

Demographics
- Consent
- Diagnosis
- Race

Family History
- Parents
- Siblings

Initial Testing
- NBS
- Genotype

Health History
- Prenatal
- Neonatal

Health History
- Immunizations
- Sick Visits
- Procedures

Exam
- Growth
- Development

Treatment
- Pharmacotherapy
- Nutrition
- Therapy

Ancillary
- Care Coordination
- Education
- Emergency Management

Studies
- Labs
- Home Monitoring
- Imaging

Pulmonary

PT

Neurology

Study Status

Today

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Secure Informatics Infrastructure

Level 1

- Public Resources – Low Restriction
- VRDBS Search
- LPDR Index
- Data Almanac - CDEs
- Case Report Forms

Level 2

- Highly Restricted
- Grantee Controlled Data
- Grantee Generated Published Data
- Case Level Data

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Current Efforts

Joint Committee
- Common Data Elements (CDEs)
- RUSP Conditions
- Subject Matter Experts
- Applicable for Research and Public Health

NBSTRN
- Informatics Infrastructure
- Disease Specific and Candidate Conditions CDEs
- Clinical Integration Workgroup
- Pilots and Grantees

NCC
- Public Health Focus
- Leveraging the Regional Genetics Collaboratives
- NCC/RC LTFU Data Workgroup
- Pilots

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NCC LTFU Effort

- The ideal implementation of LTFU in state NBS programs residing in state health departments requires the adoption of a common set of questions and answers that will be collected across all conditions.

- A set of common data elements (CDEs) enables the aggregation, analysis, sharing and reporting of information across conditions and state NBS programs.
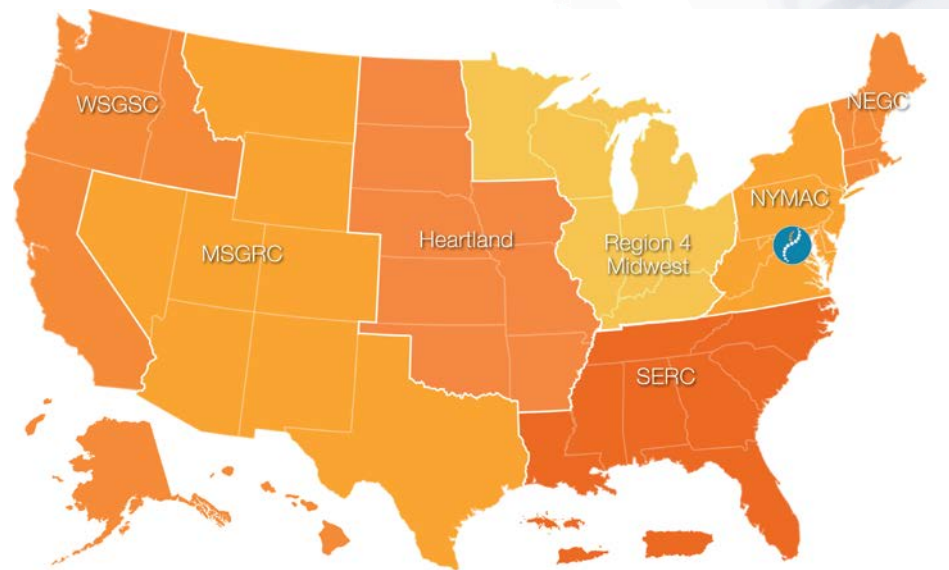
Public Health Focus

Goals

- Coordinate and accelerate LTFU efforts within public health
- Develop CDEs for public health
- Pilot public health data set
- Identify barriers

Tool

- Consensus Questions
- LPDR Overlay
- Overarching Questions

Pilot

- LPDR Public Health
- Recruit within RCs
- Identify implementation issues
- Inform future efforts

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Consensus Questions

1   Is the disorder on the newborn panel?

2   What percent of children with disorders remain in care between the ages of one and five years old?

3   What percent become lost to follow-up?

4   What percent of parents refuse treatment?

5   What percent died due to problems associated with this disorder?

6   What percent were determined not to need ongoing treatment?

7   What percent of children (combined or by specific type of disease) had age appropriate developmental status with respect to speech, physical development, mental/cognitive development, gross motor and fine motor development?

8   What percent of children were severely delayed with respect to any of the developmental measures and what year of life did the delays become apparent?

9   What percent of patients experienced symptoms associated with their disorder and at what age did the symptoms become apparent?

10 In any given year, what percent of children experienced the loss of skills they had previously acquired?

11 What percent of children had no hospitalizations or emergency room visits in the previous year of life?

12 What disorders are associated with the greatest number of hospitalizations and emergency room visits due to disorder-related complications?

13 What disorders are associated with the highest utilization of metabolic center visits?

14 What percent of children are receiving a multidisciplinary team of services, including nutritional counseling, health education and social services?
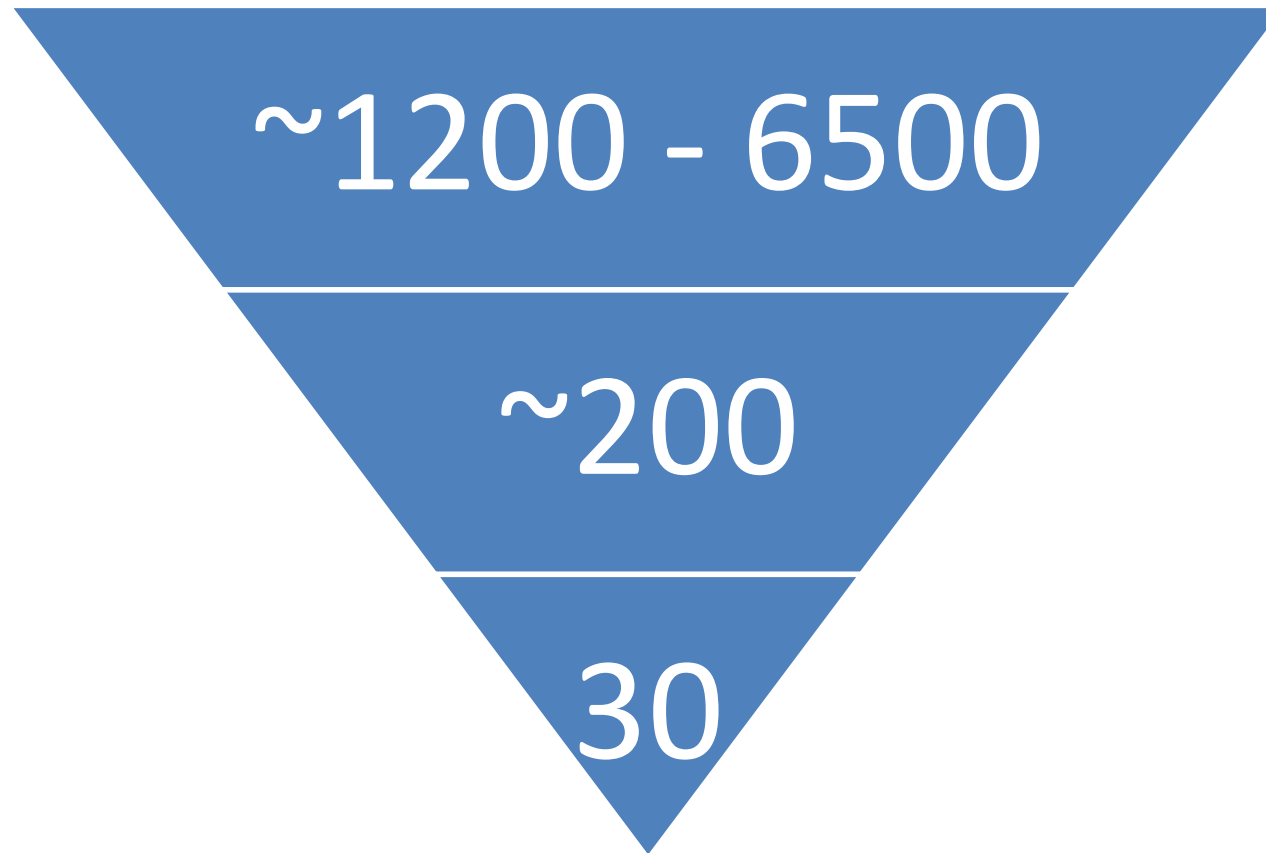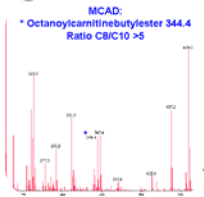
Source of Desired Information

Prenatal Education

Screening

Diagnosis and Short-Term Follow-Up

Clinical Care and Long-Term Follow-Up

Clinical Care

Research

Public Health

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- Discussion

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Case Studies

SCID
- Clinical Heterogeneity
- Diagnoses
- Follow-Up

**Genomics**
- NICU
- Health Population

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Case Studies

SCID
- Clinical Heterogeneity
- Diagnoses
- Follow-Up

Genomics
- NICU
- Health Population

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Severe Combined Immune Deficiency

- SCID and related T-cell lymphocyte deficiencies are a group of disorders

- Characterized by lack of functioning immune system

- Classic SCID is universally fatal in the first two years without immune reconstitution

- Early diagnosis is essential for lifesaving treatment

- Recommended to the RUSP January 2010

- Adopted to the RUSP May 2010

- Currently ~70% of newborns screened
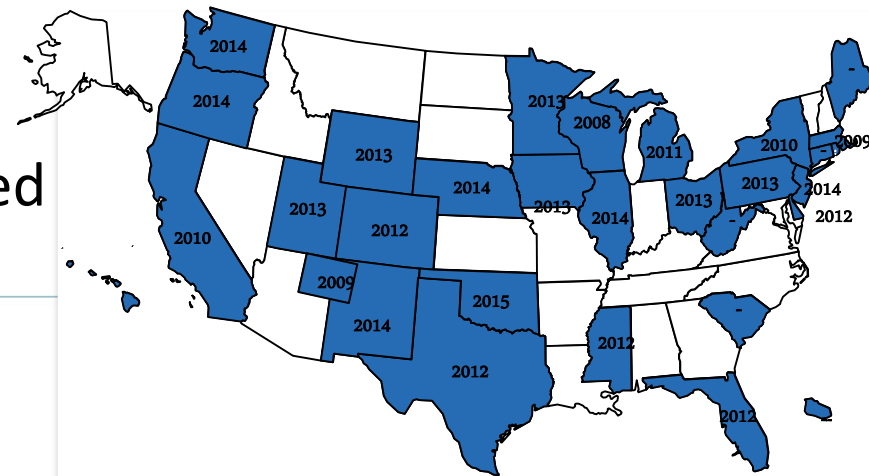
Pilots of Newborn Screening
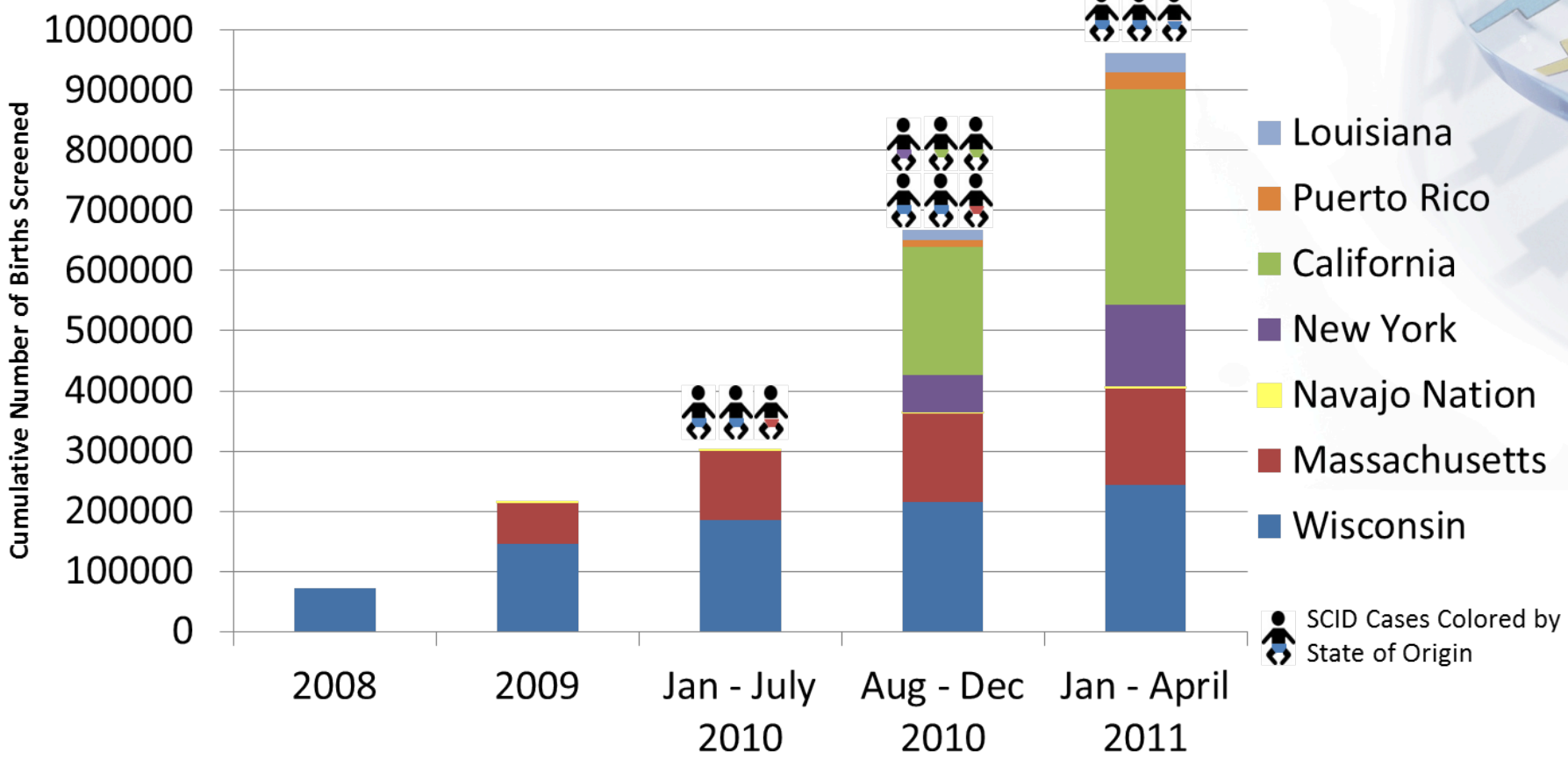
Utilization of NBSTRN Tools

Core
- Coordinate meetings of SCID experts in NBS, diagnosis, and management
- Translate findings to state programs, clinicians and other stakeholders
- Host monthly stakeholder calls and webinars

VRDBS
- Mechanism to make screen positive samples available to researchers
- Samples = 173
- Clinical diagnoses = 6

LPDR
- Clinical case report forms and system to collect information
- Diagnosis categories for screen positive
- Screened = 3,030,083 Cases = 52

R4S
- Analytical and clinical validation of screening technology
- Data elements captured = 28
- Submitters = 83   Cases = 177

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Report of 11 Programs

- Objectives
  - To present data from a spectrum of SCID newborn screening programs, establish population-based incidence for SCID and other conditions with T-cell lymphopenia, and document early institution of effective treatments.

- Results
  - Screening detected 52 cases of typical SCID, leaky SCID, and Omenn syndrome, affecting 1 in 58 000 infants.
  - Survival of SCID-affected infants through their diagnosis and immune reconstitution was 87%(45/52), 92%(45/49) for infants who received transplantation, enzyme replacement, and/or gene therapy

- Conclusions
  - Newborn screening in 11 programs in the United States identified SCID in 1 in 58 000 infants, with high survival. The usefulness of detection of non-SCID T-cell lymphopenias by the same screening remains to be determined.

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IMPORTANCE Newborn screening for severe combined immunodeficiency (SCID) using assays to detect T-cell receptor excision circles (TRECs) began in Wisconsin in 2008, and SCID was added to the national recommended uniform panel for newborn screened disorders in 2010. Currently 23 states, the District of Columbia, and the Navajo Nation conduct population-wide newborn screening for SCID. The incidence of SCID is estimated at 1 in 100 000 births.

OBJECTIVES To present data from a spectrum of SCID newborn screening programs, establish population-based incidence for SCID and other conditions with T-cell lymphopenia, and document early institution of effective treatments.

DESIGN Epidemiological and retrospective observational study.

SETTING Representatives in states conducting SCID newborn screening were invited to submit their SCID screening algorithms, test performance data, and deidentified clinical and laboratory information regarding infants screened and cases with nonnormal results. Infants born from the start of each participating program from January 2008 through the most recent evaluable date prior to July 2013 were included. Representatives from 10 states plus the Navajo Area Indian Health Service contributed data from 3 030 083 newborns screened with a TREC test.

MAIN OUTCOMES AND MEASURES Infants with SCID and other diagnoses of T-cell lymphopenia were classified. Incidence and, where possible, etiologies were determined. Interventions and survival were tracked.

RESULTS Screening detected 52 cases of typical SCID, leaky SCID, and Omenn syndrome, affecting 1 in 58 000 infants (95% CI, 1/46 000-1/80 000). Survival of SCID-affected infants through their diagnosis and immune reconstitution was 87% (45/52), 92% (45/49) for infants who received transplantation, enzyme replacement, and/or gene therapy. Additional interventions for SCID and non-SCID T-cell lymphopenia included immunoglobulin infusions, preventive antibiotics, and avoidance of live vaccines. Variations in definitions and follow-up practices influenced the rates of detection of non-SCID T-cell lymphopenia.

LPRD

R4S

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Current Case Studies

SCID
- Clinical Heterogeneity
- Diagnoses
- Follow-Up

Genomics
- NICU
- Healthy Population

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"Genomic sequencing has potential to diagnose a vast array of disorders and conditions at the very start of life. But the ability to decipher an individual's genetic code rapidly also brings with it a host of clinical and ethical issues, which is why it is important that this program explores the trio of technical, clinical, and ethical aspects of genomics research in the newborn period."

Alan Guttmacher, MD, Director of NICHD

Four Pilot Projects

Brigham and Women's Hospital and Boston Children's Hospital	Children's Mercy Hospital, Kansas City	University of California, San Francisco	University of North Carolina at Chapel Hill
Impact and usefulness of genomic data throughout infancy and childhood	Benefits and risks of using genomic information in the NICU	Exome sequencing for RUSP and candidate conditions	Examine exomes of infants with known genetic conditions and determine best way to return results to doctors and parents

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Goals of Collecting CDEs

- Types of research
  - Gene discovery
  - Phenotype spectrum of rare variants
  - Modifying genes for metabolic conditions
  - PGx studies

- Research across NSIGHT
  - Across all groups
  - Between 2 or 3 groups

- Research across NBSTRN

- Contribute to other efforts – ClinGen/ClinVar

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4 Different Study Designs

- BWH/BCH/BCM
  - NICU population
  - Healthy newborns

- Children's Mercy
  - NICU population

- UNC
  - Affected cohort with diagnosed metabolic conditions
  - Healthy newborns

- USF
  - De-identified newborn blood spots linked to clinical data
  - Patients suspected of having a primary immunodeficiency not identified by newborn screening

Approach to CDE Sharing

- "Above and below the line" approach to identify CDEs
  - Shared with NBSTRN LPDR
  - Shared among NSIGHT Teams
  - NSIGHT Team only

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Acknowledgements

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Hans Andersson, MD
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Acknowledgements

- **Clinical Integration Group**
  - Cynthia Powell
  - Deborah Garner
  - Debra Freedenberg
  - Dwight Koeberl
  - Janet Thomas
  - Kathryn Hassell
  - Kathryn Swoboda
  - Lisa Feuchtbaum
  - Melissa Wasserstein
  - Michele Caggana
  - Michele Puryear
  - Susan Berry
  - Thomas Langan
  - Tiina Urv

- **NCC/RC LTFU Workgroup**
  - Adrya Stembridge
  - Ana H. Morales
  - Andrea Lewis
  - Beth Hannan
  - Christelle Farrow
  - Connie Turney
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  - Gina Gembel
  - Janet Thomas
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