NBSTRN
Newborn Screening Translational Research Network

Newborn Screening Pilot Studies in the Newborn Screening Translational Research Network (NBSTRN)

February 12, 2015
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The **Newborn Screening Translational Research Network (NBSTRN)** seeks to improve the hea outcomes of newborns with genetic or congenital disorders through an infrastructure that provides the research community access to robust newborn screening resources.

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Newborn Screening Research Tools

What's New

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Newborn Screening Saves Lives Act Reauthorization

- Section 6 authorizes the Secretary to expand the Hunter Kelly Newborn Screening Research Program to:
  - provide research and data for newborn conditions under review by the Advisory Committee to be added to the Recommended Uniform Screening Panel, and
  - conduct pilot studies on conditions recommended by the Advisory Committee to ensure that screenings are ready for nationwide implementation.

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NBSTRN Pilots

- Infrastructure for NBS clinical validation pilots
- Severe Combined Immunodeficiency Disorders
- SMA
- **N**ewborn **S**creening **i**n **G**enomic Medicine and Public **H**eal**t**h (NSIGHT)
- Pompe Disease
  - Other Lysosomal Storage Diseases
- Some of what is coming

Research Tools

- Virtual Repository of Dried Blood Spots (VRDBS)
- Laboratory Performance Database (R4S)
- Long Term Follow-Up Data Collection

Laboratory Performance Database (R4S)

The Laboratory Performance Database (Region 4 Stork - R4S) project is the partnership and adaptation of Region 4 Laboratory Performance Database to Support NBSTRN newborn screening laboratory pilot testing. It is the integration of the analytical pilot study data for newborn screening studies into the existing Region 4 Collaborative's Laboratory Performance Program Database (R4S).

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NBSTRN Tools

VRDBS

- The **Virtual Repository of Dried Blood Spots (VRDBS)** is an open-source, web-based tool that enables NBS researchers to search over 2 million DBS from participating states.

LPDR

- 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.

R4S

- 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.

Common Information Data Set

- Four domains (and federal agencies) of interest in data; one source of data
  - Surveillance
  - Public health
  - Patient care
  - Knowledge generation
- Datasets are complete for all conditions in NBS including common and disease specific elements
  - Data dictionaries are being approved through NLM to become a part of the standard EMR systems of manufacturers
- Currently working with states to identify data that will inform their own program interests in clinical service utilization, outcomes, etc.

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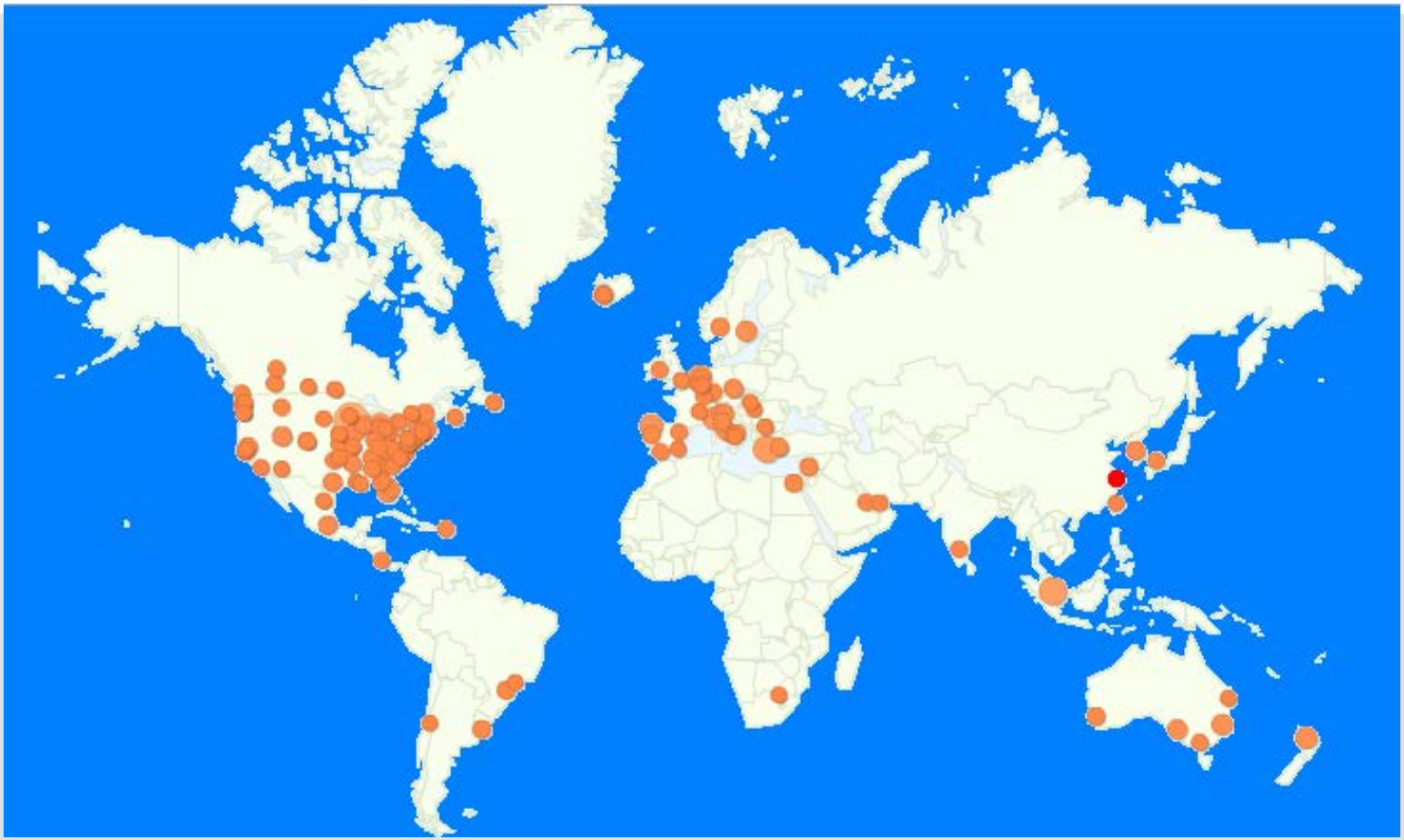
R4S Supports Multistate Collaboration in Pilot Studies in NBS

- Web-based database for the collection and display of data from true positive patients found in newborn screening
- Allows:
  - Quality improvement of NBS
  - Discovery of new markers for screened conditions
  - Prospective collection of data in pilot tests for:
    - New conditions
    - New technologies (e.g., comparative research)

Region 4 Stork (R4S)
135 Participating Sites (World)



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

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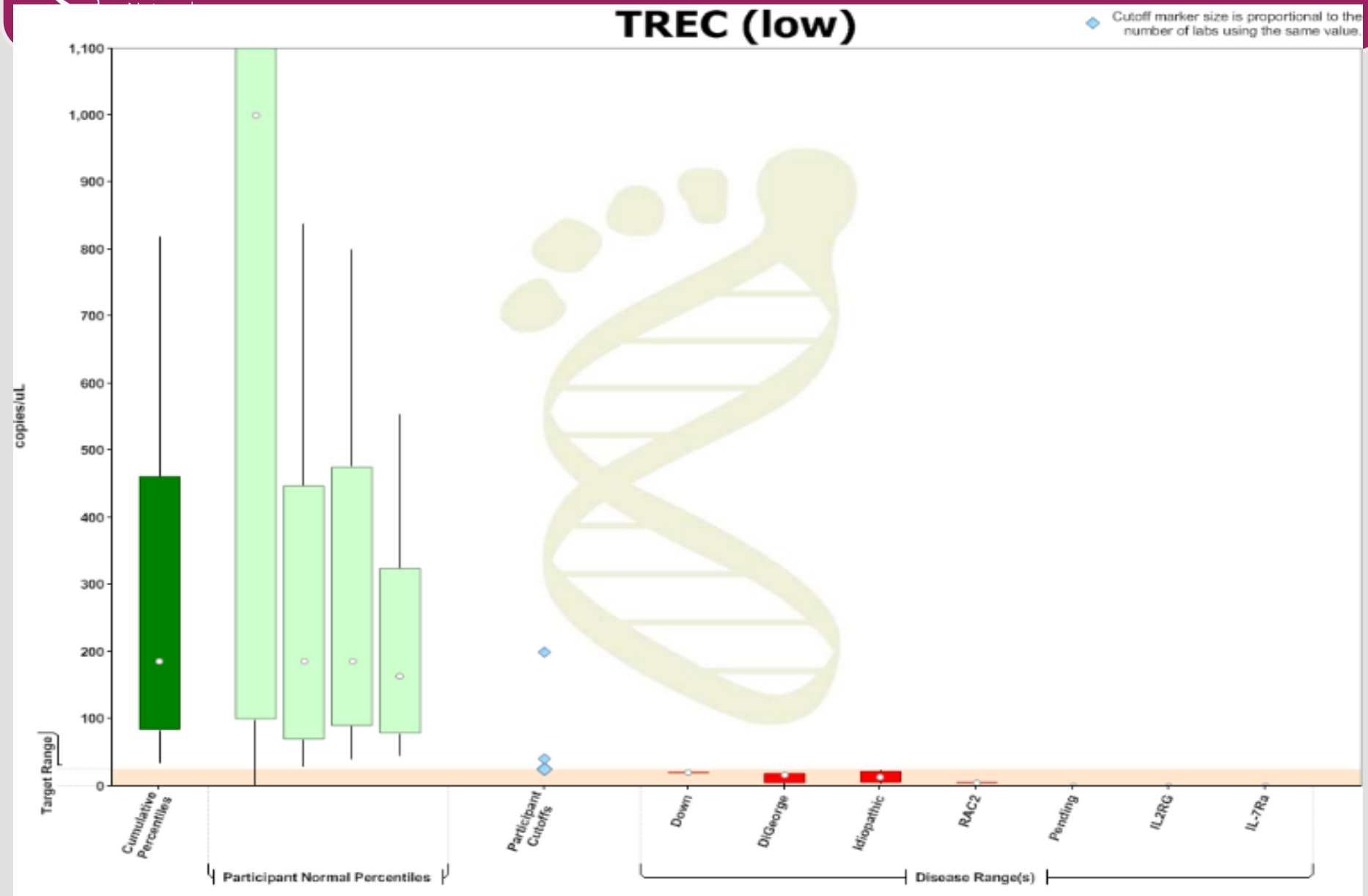
Newborn Screening
Translational Research

SCID Collaborative Pilot



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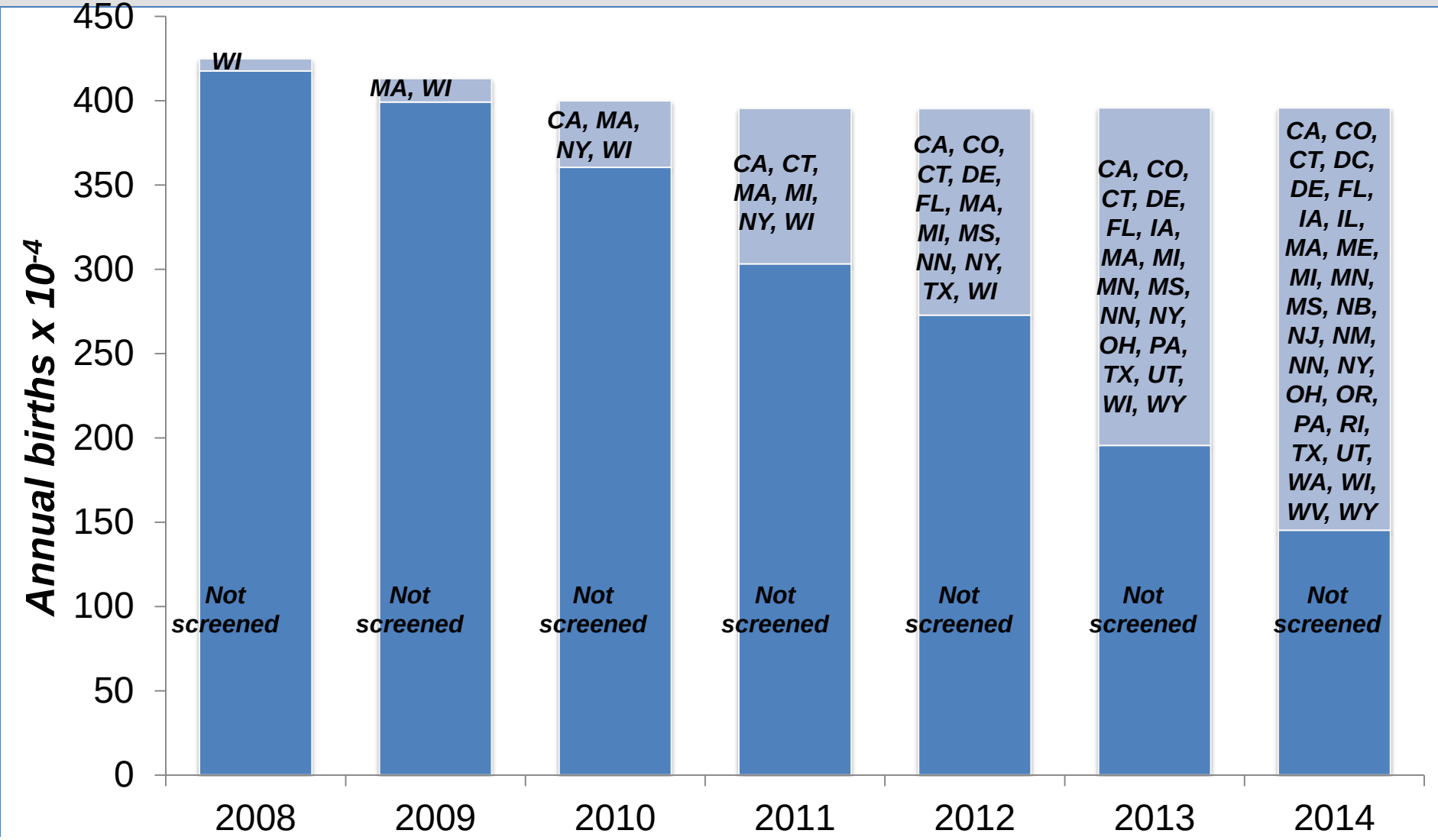
Adoption of SCID Newborn Screening in U.S. as of 2014



Courtesy of Jennifer Puck and Antonia Swan, UCSF

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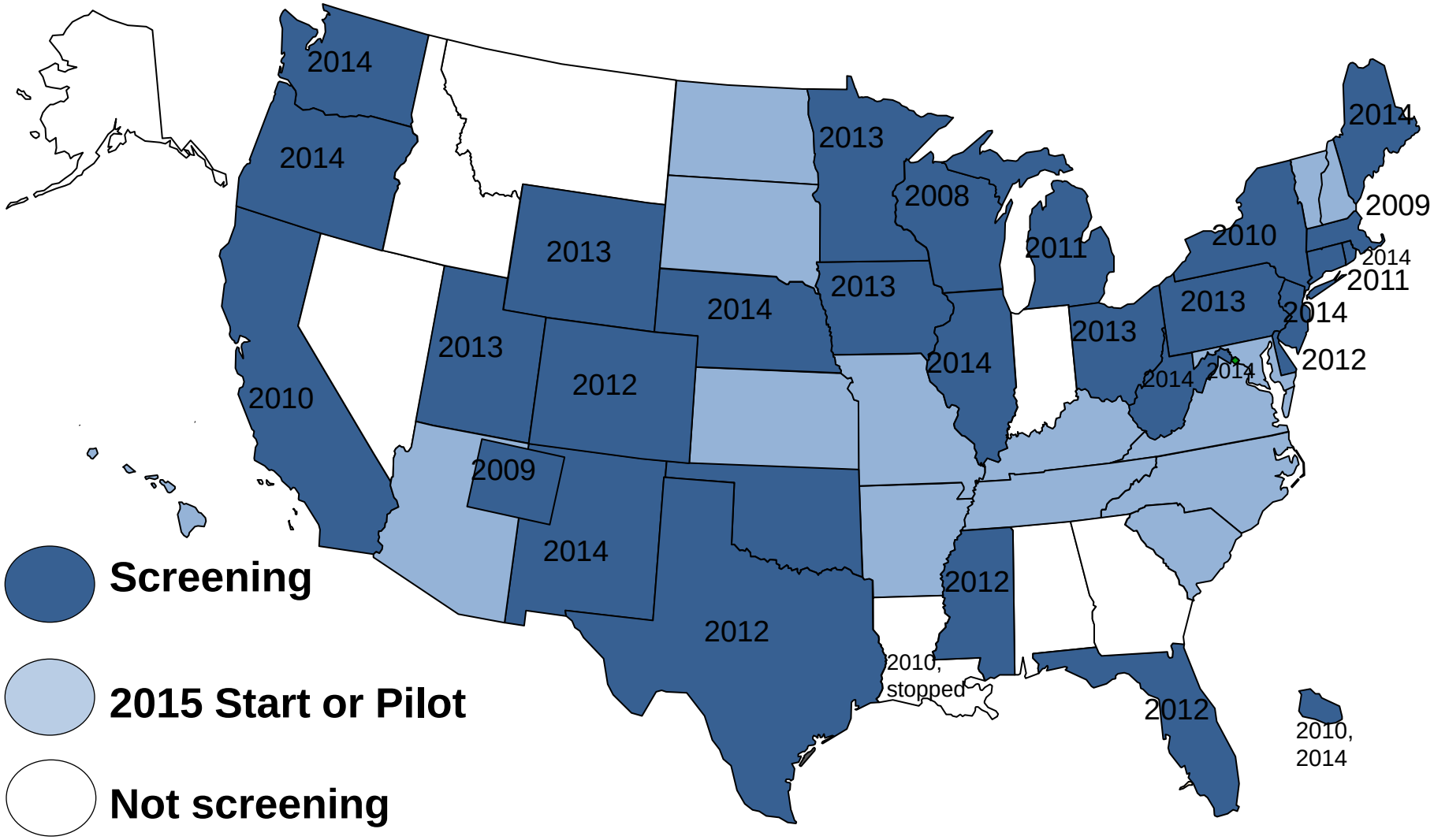
SCID Newborn Screening January 2015



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4 Years of California SCID Newborn Screening (2010-2014)

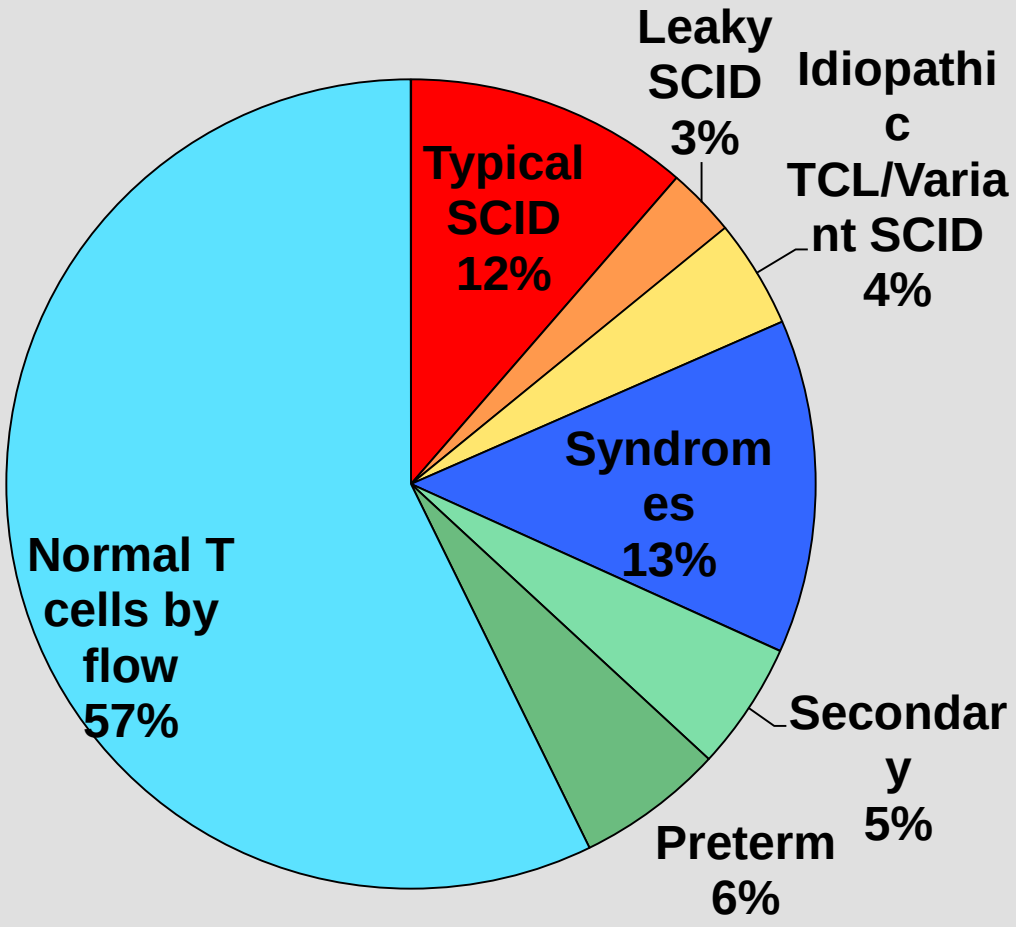
1,980,133 infants screened

1.3 infants per 10,000 (255) required flow cytometry

109/255 had <1500 T cells/uL (43%)

<u>1/55,000 SCID (Typical and Leaky)</u>

1/180,000 idiopathic TCL



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Non-SCID Conditions Detected with Low TRECs

- Multisystem syndromes with variable T cell deficiency
  - 57% DiGeorge/chromosome 22q11.2 deletion
  - 15% Trisomy 21
  - 3% Ataxia telangiectasia
  - 2% CHARGE syndrome
- Secondary T lymphopenia
  - 25% Congenital cardiac anomalies
  - 38% Other congenital anomalies
  - 13% Vascular leakage, third spacing, hydrops
  - 3% Neonatal leukemia
- Extreme preterm birth—T cells become normal over time
- “Variant SCID” or Idiopathic T lymphopenia—few naïve T cells, no maternal engraftment, impaired T cell or antibody responses, no known gene defect

Courtesy of Jennifer Puck and Antonia Swan, UCSF

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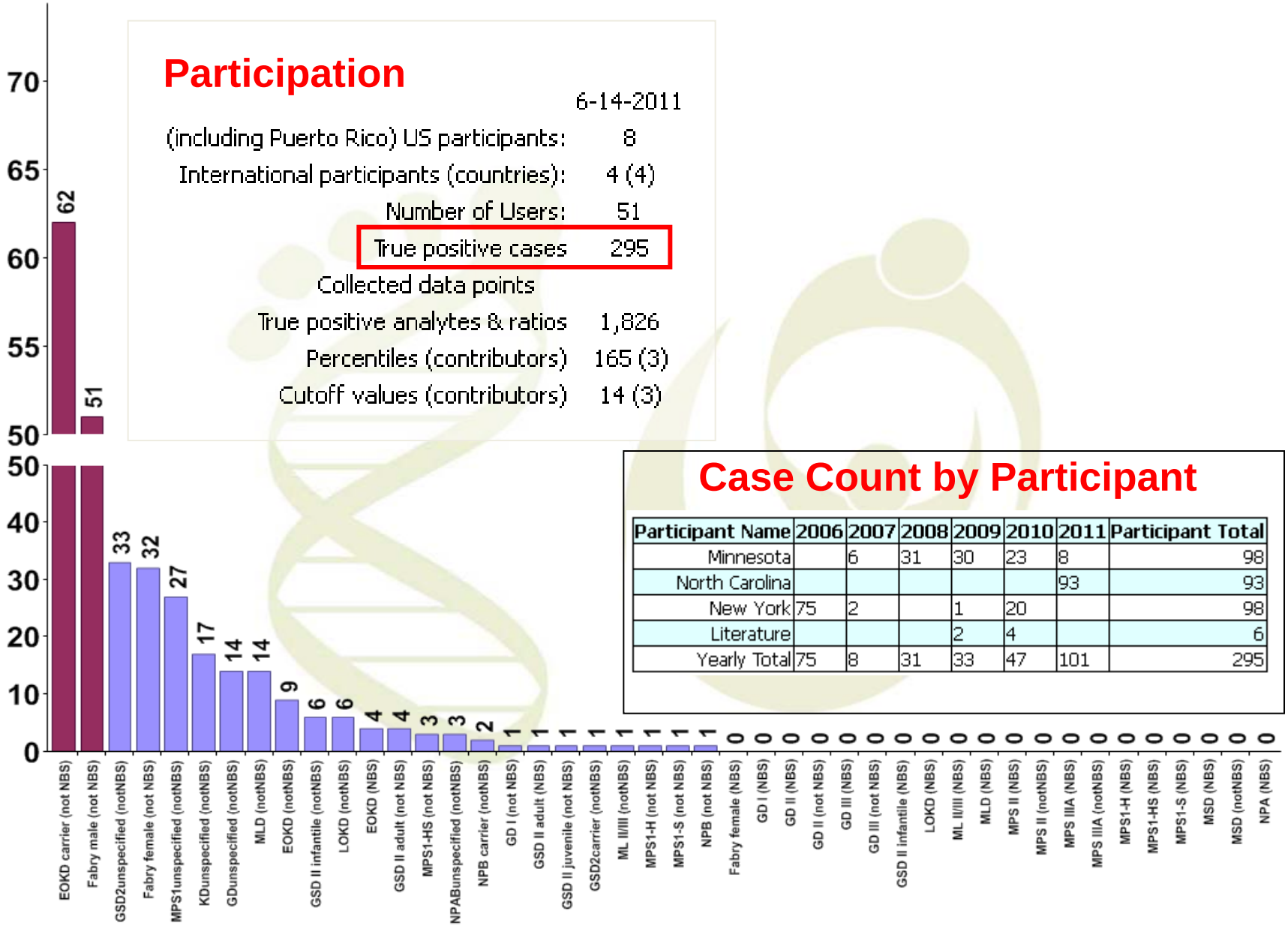
Pompe Disease Pilot

- NICHD-funded to screen 400,000 babies
- States funded
  - Georgia (Emory)
  - New York began screening on October 1, 2014
  - Wisconsin
- Others
  - Illinois began in 4 hospitals
  - Missouri began screening in November 2013
- Broader LSD pilot (Melissa Wasserstein in NBSTRN)

LSD COLLABORATIVE PROJECT

Participation

	6-14-2011
(including Puerto Rico) US participants:	8
International participants (countries):	4 (4)
Number of Users:	51
True positive cases	295
Collected data points	
True positive analytes & ratios	1,826
Percentiles (contributors)	165 (3)
Cutoff values (contributors)	14 (3)



Case Count by Participant

Participant Name	2006	2007	2008	2009	2010	2011	Participant Total
Minnesota		6	31	30	23	8	98
North Carolina						93	93
New York	75	2		1	20		98
Literature				2	4		6
Yearly Total	75	8	31	33	47	101	295

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Unknowns

- Newborn Screening Saves Lives Act
  - Consent for use of residual dried blood spots in research after March 18, 2015
  - OHRP to
- FDA
  - Laboratory developed tests (LDTs) and NBS
  - Involvement in research

- Section 9 - Directs HHS to update the Federal Policy for the Protection of Human Subjects, also known as the Common Rule, not later than two years after enactment of this Act. Applies the following provisions until HHS updates the Common Rule:
  - requires federally funded research on newborn dried blood spots to be considered research on human subjects (which requires the informed consent of the subject), and eliminates the ability of an institutional review board to waive informed consent requirements for research on newborn dried blood spots.

Uniform Screening Panel (2015)

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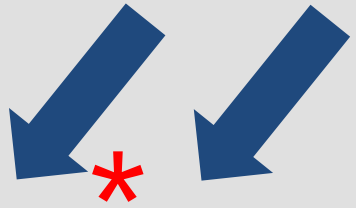
- 31 primary conditions
  - 20 detected by MS/MS (AA, FAO, OA)
  - 3 Hemoglobinopathies (S/S, S/βThal, S/C)
  - 9 others (BIOT, CAH, CF, CH, GALT, HEAR, SCID*, CCHD*)
- 26 secondary targets
  - 22 detected by MS/MS (AA, FAO, OA)
  - 1 Hemoglobinopathy (many variants counted as
  - 3 others (GAL-epimerase, GAL-kinase, other T-cell def.)



*Critical congenital heart defect

Uniform
Panel

57

Partial List of Candidate Conditions for Expansion of Newborn Screening

Uniform Panel

74

- ALD (X-linked)
- CDG Ib
- CMV
- Creatine defects
- DMD
- G6PD
- HIV
- Fam. Hypercholesterol.
- Fragile X
- Friedreich's ataxia
- LSD
- Proximal UCDs
- SLO
- SMA
- Toxoplasmosis
- Wilson disease

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Partial List of Candidate Conditions for Expansion of Newborn Screening

Uniform Panel

87

- Fabry disease (X-linked)
- Gaucher disease
- Krabbe disease
- Metachrom. Leukodystr. (MLD)
- Pseudo MLD
- MPS I
- MPS II
- MPS IIIA
- MPS VI
- Mucolipidosis type II/III
- Multiple sulphatase deficiency
- Niemann–Pick disease type A/B
- Pompe disease

- Fragile X
- Friedreich's ataxia
- LSD
- Proximal UCDs
- SLO
- SMA
- Toxoplasmosis
- Wilson disease

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Partial List of Candidate Conditions for Expansion of Newborn Screening

Uniform Panel

100+

- ALD (X-linked)
- CDG Ib
- CMV + 4 AD Genes
- Creatine defects
- DMD
- G6PD
- HIV
- Fam. Hypercholesterol.

- ALD carriers
- Zellweger sdr
- Other DPBs
- CRT (X-linked)
- CRT carriers
- GAMT
- AGAT

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Preparing for the Onslaught

- Capacity building
- Resolution of unclear boundaries between NBS quality improvement vs. translational practice vs. research
- New opportunities
  - Precision Medicine Initiative
  - Ability to prospectively characterize clinical histories
- Integration into a learning health care system

Thanks