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

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Michael Watson, MS, PhD, FACMG
The Newborn Screening Translational Research Network (NBSTRN) seeks to improve the health outcomes of newborns with genetic or congenital disorders through an infrastructure that provides the research community access to robust newborn screening resources.

Building a research infrastructure for a healthier world.
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.
NBSTRN Pilots

- Infrastructure for NBS clinical validation pilots
- Severe Combined Immunodeficiency Disorders
- SMA
- Newborn Screening in Genomic Medicine and Public Health (NSIGHT)
- Pompe Disease
  – Other Lysosomal Storage Diseases
- Some of what is coming
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).
- 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.

- 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 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.
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)
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
SCID Collaborative Pilot

TREC (low)

Cutoff marker size is proportional to the number of labs using the same value.
Adoption of SCID Newborn Screening in U.S. as of 2014

Year | Annual births x $10^{-4}$ |
--- | --- |
2008 | Not screened |
2009 | Not screened |
2010 | Not screened |
2011 | Not screened |
2012 | Not screened |
2013 | Not screened |
2014 | Not screened |

Not screened states:
- CA, WI, MA, NY
- CA, CT, MA, MI, NY, WI
- CA, CO, CT, DE, FL, MA, MI, MS, NY, WI
- CA, CO, CT, DE, FL, IA, MA, MI, MS, NN, NY, OH, PA, TX, UT, WI, WY
- CA, CO, CT, DC, DE, FL, IA, IL, MA, ME, MI, MN, MS, NB, NJ, NM, NN, NY, OH, OR, PA, RI, TX, UT, WA, WI, WV, WY

Courtesy of Jennifer Puck and Antonia Swan, UCSF
1,980,133 infants screened

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

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

1/55,000 SCID (Typical and Leaky)

1/180,000 idiopathic TCL

Typical SCID 12%
Leaky SCID 3%
Idiopathic TCL/Variant SCID 4%
Syndromes 13%
Secondary 5%
Preterm 6%
Normal T cells by flow 57%

Courtesy of Jennifer Puck and Antonia Swan, UCSF
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
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)
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

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<th>Participant Name</th>
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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.
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.)
Partial List of Candidate Conditions for Expansion of Newborn Screening

- 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
Partial List of Candidate Conditions for Expansion of Newborn Screening Uniform Panel

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

- 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
Partial List of Candidate Conditions for Expansion of Newborn Screening

- 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

100+
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