Newborn Screening Translational Research Network Update
Heartlands Regional Genetics and Newborn Screening Collaborative
October 4, 2012

Overview

- Introduction of New Members
- Review of NBSTRN-CC Work Group Activities
  - Legal and Bioethics
  - NBS Laboratories and Programs
  - Clinical Centers
    - Data Access, Sharing, and Use Limitations
  - IT and Informatics
    - Website
    - VRDBS
    - LTFU data sets
    - R4S
- NBSTRN Pilots
  - LSDs
  - SCID
Overview (continued)

- NBSTRN Program Grantees
  - Spinal muscular atrophy: PI - Kathy Swoboda
  - Metabolic disease in NBS: PI Sue Berry and Cynthia Cameron
  - Newborn Screening for Lysosomal Storage Diseases: PI - Melissa Wasserstein

- NBSTRN Program Contractees
  - LSD comparative evaluation of NBS technologies: PI - Dieter Matern
  - SMA / SCID NBS technologies: PI - Steve Dobrowolski
  - NBSTRN-CC pilots to assess infrastructure and data systems
    - SCID
    - LSDs

Coordinating Center Organization

Coordinating Center
- Michael Watson, Project Director
- Barry Thompson, Medical Director
- Amy Hoffman, Project Manager
- Amy Brower, Genomics Scientist
- Bruce Bowdish, IT Manager
- Inna Smotrich, Project Coordinator
- Sophie Stich, Administrative Assistant
- Louis Hoffman, Systems Analyst

Standing Committee
- Harvey Levy
- Susan Berry

Clinical Centers
- Susan Berry
- Kathy Hassell

Laboratories
- Stan Berberich
- Steve Dobrowolski

Bioethics & Legal Issues
- Ed Goldman
- Jeff Brosco

FISMA Control Board
- ACMG Coordinated
### Workgroups

<table>
<thead>
<tr>
<th>Workgroup</th>
<th>Focus</th>
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</table>
| Clinical Centers   | • Consensus data set  
                    | • Disease specific data sets  
                    | • Data capture tool  
                    | • Data access and governance  
                    | • Support grantees |
| Laboratory         | • New technology development and validation  
                    | • New test validation |
| Bioethics & Legal  | • IRB 101 for investigators and IRBs  
                    | • Model consent form modules  
                    | • Describe patient protections |
| Information        | • Data capture tool  
                    | Technology |
| Information Technology | • Data management system  
                    | • Change control board  
                    | • Data display tools for comparative research |

### NBSTRN Key Resources

#### Patient/Subject/Case

<table>
<thead>
<tr>
<th>Screening</th>
<th>Short-Term Follow-Up and Diagnosis</th>
<th>Long-Term Follow-Up and Clinical Management</th>
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<tbody>
<tr>
<td>State Public Health Laboratory</td>
<td>State Public Health STFU</td>
<td>State Public Health LTFU</td>
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</table>

| Medical Home, Clinician, Specialist |

#### Analytical Data

<table>
<thead>
<tr>
<th>Technology</th>
<th>Treatments</th>
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<tr>
<td>Investigator, Researcher, Grantee</td>
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<table>
<thead>
<tr>
<th>DBS Specimens</th>
<th>Research Cohorts</th>
<th>LTFU Data Capture</th>
<th>LTFU Database</th>
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<tbody>
<tr>
<td>Characterized Biospecimens</td>
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</table>
NBS Legal and Bioethics Work Group

- Web site (NBSTRN and VRDBS) content recently revised
- Addressing new issues arising from grantees
  - SMA early lethality and need to identify patients as newborns to understand clinical history
  - Opt-in vs. opt-out consent
- Developing research agenda for NBS
- Considering a consultation function

NBS Laboratories and Programs Work Group

- Biospecimen Repositories
  - Virtual Repository of Dried Blood Spots (VRDBS)
    - Conditions in NBS
    - Unaffected
    - Cohorts from prior NBS research projects
    - Opened September 2012
  - Patient specimens
    - Consent to obtain dried blood spot punch
Current VRDBS Totals for 4 States

Over 2.2 Million Entries

- General Population
- Not RUSP
- RUSP

Newborn Screening Translational Research Network

Current Data

Search Results

<table>
<thead>
<tr>
<th>State</th>
<th>Stored Specimens</th>
<th>Qty Requested</th>
<th>Usage Restrictions</th>
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<tbody>
<tr>
<td>California</td>
<td>258,483</td>
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<td>DBS Specimen Use Restrictions</td>
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<tr>
<td>Iowa</td>
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<td>DBS Specimen Use Restrictions</td>
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<td>Michigan</td>
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<td>DBS Specimen Use Restrictions</td>
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<tr>
<td>New York</td>
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<td>DBS Specimen Use Restrictions</td>
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</table>

Iowa: past five years excluding the most recent 12 months – updated monthly
New York: 2007 – present – updated every 6 months
California: cases 2006 – present (6 mo lag) negatives from last 6 months – updated every 6 months
### VRDBS Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th># DBS</th>
<th>Condition</th>
<th>#DBS</th>
<th>Condition</th>
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<th>Condition</th>
<th>#DBS</th>
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<tr>
<td>General Pop</td>
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<td>3-MCC</td>
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<td>CBL C</td>
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<td>Hb S</td>
<td>3,073</td>
<td>CAH (SW)</td>
<td>211</td>
<td>CAH (NC)</td>
<td>43</td>
<td>ASA</td>
<td>15</td>
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<td>CH</td>
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<td>PKU</td>
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<td>LCHAD</td>
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<td>Other Hb w/out Hb S</td>
<td>937</td>
<td>SCAD</td>
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<td>CAH (SV)</td>
<td>40</td>
<td>TYR-1</td>
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<td>CF</td>
<td>733</td>
<td>BIO</td>
<td>106</td>
<td>CH2</td>
<td>37</td>
<td>CIT-I</td>
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<td>Hb Barts/Alpha Thal</td>
<td>296</td>
<td>GALT</td>
<td>92</td>
<td>IVA</td>
<td>33</td>
<td>CAH (11B-OHD)</td>
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<td>TBG</td>
<td>279</td>
<td>CUD</td>
<td>76</td>
<td>MSUD</td>
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<td>MCAD</td>
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<td>VLCAD</td>
<td>68</td>
<td>GA-2</td>
<td>18</td>
<td>CPT-II</td>
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<td>Beta Thal w/out Hb S</td>
<td>248</td>
<td>MUT</td>
<td>62</td>
<td>PROP</td>
<td>16</td>
<td>HCY</td>
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<tr>
<td>H-PHE</td>
<td>214</td>
<td>GA-1</td>
<td>51</td>
<td>MET</td>
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</table>

### New Infrastructure and Resources

- **Research cohorts in VRDBS**
  - LSDs
  - MPS
  - Fra(X)
  - Cerebrotendinous xanthomatosis
  - SCID

- **Clinical Centers and Standing Committee guidance on conditions to prioritize for research cohort development**
Update on Informatics Tools and Resources

- **R4S – Laboratory Quality Improvement of Newborn Screening**
  - Analytical Validation
  - Clinical Validation
  - Pilots

- **Long-term and Effective Follow-up**
  - Common Data Elements
  - Disease Specific Data Elements
  - Standardization
  - Data Almanac
  - Data Capture Tool
  - Data Management
  - Pilots

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Two Resources

- **R4S**
  - Newborn screening tests are usually performed in public health laboratories using laboratory developed tests
  - The majority of conditions screened are rare and data aggregation is needed to enable analytical validation
  - Diagnosis of conditions in newborns who screen positive occurs within the clinical health environment and is a key component of clinical validation

- **Long-Term and Effective Follow-Up Data**
  - The majority of NBS conditions require lifelong treatment and clinical care management
  - There is no coordinated data collection to advance understanding of clinical outcomes, develop new treatments and technologies
  - Patients are seen in a variety of clinical settings including specialty care, family practice and pediatrics
  - Use of existing data standards is important to enable data sharing
To facilitate analytical and clinical validation of new and existing technologies

A database and suite of analysis tools

To support newborn screening research through the development of new technologies, new conditions and new treatments

Data sets, standards, capture tool and data resource

Two New Resources

Newborn Screening Translational Research Network

R4S

Welcome to the Newborn Screening Domain

- MS/MS
- CAM
- BIOT
- SCID
- LSD
- ALD
- FRDA
- WD

Objective

To facilitate analytical and clinical validation of new and existing technologies

Resource

A database and suite of analysis tools
R4S - Analytical Data

- 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
- 130 sites in 45 countries
- Over 25K data points and over 565K analyte results in 64 conditions
- Migrated to ACMG July 2012

Pilots

- Validation of new screening technologies
- Development of modules to support NBSTRN pilot research efforts
  - Lysosomal Storage Disorders
    - Protocols
    - Disease Definitions
    - Analysis Tools
  - Severe Combined Immune Deficiency
    - Disease Definitions
    - Diagnosis
    - Analysis Tools

SCID: 56 Cases
- Lit
- CA
- NY
- Taiwan

LSD: 983 Cases
- Lit
- MN
- NC
- NY
- Taiwan
Clinical Centers Work Group

- Datasets for condition in NBS nearing completion
  - Adapting data needs of new grantees to existing data sets
  - Ongoing facilitation of standardization of laboratory and clinical languages for grantees
- Shifting to data access, sharing, and use limitation recommendations and policies for NBSTRN
  - What all users must do
  - What all users must address for their projects
  - State public health authority and access to data
- Diagnostic confirmation requirements for research cohorts in VRDBS

Development of Data Capture Tool

- Goal
  - Establish a network of centralized and institutionally-enabled infrastructure to support the capture and managed storage of longitudinal clinical data
  - This data will then be used by public health, clinicians and researchers to develop treatment programs and further newborn screening research
- Subcontract to CHOP – Dr. Pete White PI
**Objectives**

- Determine the best course of treatment and disease management to maintain quality of life
- Enable data collection, analysis and mining across the lifespan by connecting research and clinical activities and data

**Resource**

- Data elements, definitions, data capture tool and management system with shared elements

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**LTFU Guiding Principles**

- **Researcher Focused**
  - Basic, Translational and Clinical Research
- **Clinician Driven**
  - What evidence and practices should advance understanding and inform screening, diagnosis, treatment and management of patients over their lifespan?
- **Multiple Stakeholders**
  - Public Health, Medical Home, Specialty Care, Patients
- **Adopt Relevant Standards**
  - Identify Areas Where Standards Would Be Helpful
- **Sustainable, Forward Looking Resource**
  - Both Evidence-based and Discovery-based
  - Linkage to NIH Resources
Potential Uses of Data Sets

- National Data Set
- Research
- Public Health
- NQF

Common & Disease Specific
- Hypothesis Driven & Generating
- Surveillance, Outcomes, Quality Assurance & Improvement
- Benchmarks

Data Management System

- User Training
- Server Maintenance
- Annual FISMA Audit and IRB Continuation
- Updated Standards and eCRFs
Coordination Framework: Compliance with Federal Regulations

NIH policies
- Applicability
- Timeliness

NBSTRN policies
- Investigators drive individual project policies
- NBSTRN indexing of data available in repository
- Publication related data should be open
- Investigators designate open non-PHI data
- Post-project data retention

NBSTRN Data Access Committee (DAC)
# Research Pilots Utilizing NBSTRN

<table>
<thead>
<tr>
<th>Pilot</th>
<th>New Test</th>
<th>New Condition</th>
<th>New Treatment</th>
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<tbody>
<tr>
<td>Severe Combined Immune Deficiency</td>
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<td>√</td>
<td></td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Inborn Errors of Metabolism</td>
<td></td>
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<td>√</td>
</tr>
<tr>
<td>Lysosomal Storage Disorders</td>
<td>√</td>
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</tr>
</tbody>
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## Grantee Update

- **NIH Awarded Grantees**
  - Cynthia Cameron and Susan Berry – Clinical history of metabolic diseases in NBS
  - Kathy Swoboda – Clinical history of SMA
  - Shunji Tomatsu – NBS for mucopolysaccharidoses
  - Eric Vilain – Clinical history of disorders of sexual development (includes CAH)
- **NIH Awarded Contracts**
  - Steven Dobrowolski – Application of calibrated molecular melting curve analysis to SCID and SMA
  - Dietrich Matern – Comparative assessment of technologies for LSD NBS
Grantees: Kathy Swoboda – NBS for spinal muscular atrophy to develop clinical history

- Screening for SMA in Utah and Colorado
  - Diagnosis and follow-up among providers in Utah and Colorado
  - Project started in April 2011
  - Screening planned to begin in April 2012
  - Developing policies with NBSTRN on recommendations for modes of consent for research involving conditions that are neither part of NBS nor immediate candidates for NBS
  - Utilizes NBSTRN repository system and patient data capture tools

Grantees: Cynthia Cameron and Sue Berry - Clinical Histories of Metabolic diseases in NBS

- Clinical history development in diagnosed cases
  - Involves 13 clinical centers in 10 states
  - Project started in April 2011 with prior history in Regional Collaborative project
  - Utilizes NBSTRN patient data capture tools
Grantee: Melissa Wasserstein
Newborn Screening Pilot for 5 LSDs

- **Screening**
  - in collaboration with New York State Lab/Program
  - 4 large hospitals in NYC
  - 80,000 babies over 4 years

- **Diagnosis and evaluation/management**
  - Using NBSTRN infrastructure

Contractor: Dietrich Matern – Comparative Assessment of NBS Screening Technologies for LSDs

- Utilizing R4S web resource
- Curating LSD pilot study data in R4S
- Dealing with complications in accessing NBS specimens in Minnesota
Contractor: Steve Dobrowolski – Application of calibrated molecular melting curve analysis to SCID and SMA

- Development of melting curve assays for SMA, SCID, CMV,....
- Needs research cohorts

Pilot Project - LSDs

- NY, IL, MO, NM initiating screening
- Working with Lysosomal Disease Network (ORD-RDCC)
- Data collection slowed by Illinois’ need to validate an alternative testing platform
Grants in Process

- Natural History of Disorders Identifiable by Newborn Screening - LSDs
- Fragile X Newborn Screening Technology
- Several prior applicants resubmitting
  - A Prospective Delineation of the Adult Galactosemic Phenotype: The Impact of Newborn Screening
  - Whole genome analysis in NBS
- How will the NBSTRN need to be modified for upcoming projects?
  - Newborn Screening and Whole Genome Sequencing RFA now open

Next Steps

- NBSTRN Annual Meeting
- Whole genome sequencing with integration with LTFU data capacity development
  - ?Other whole genome issues
- Research cohort development
Thank You and Acknowledgments

NBSTRN is funded by a contract to the American College of Medical Genetics and Genomics from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (HHSN27520080001C)

LTFU Data Sets:
• Inborn Errors Of Metabolism Collaborative (IBEMC)
• National Institute of Neurological Disorders and Stroke (NINDS)
• National Library of Medicine (NLM)
• National Coordinating Center for Regional Genetics and Newborn Screening Service Collaboratives (NCC)

Center for Biomedical Informatics, Children’s Hospital of Philadelphia

QUESTIONS?

Newborn Screening Translational Research Network