Development of Informatics Tools to Support the Long-Term Follow-Up of Individuals with Conditions Included in Newborn Screening: A Pilot Focused on Inborn Errors of Metabolism

K. Bentler presenting for S.A. Berry, S. Hiner, S. Zhai, C. Cameron, K. Hassell, J. Loutrel, A. Brower, and M. Watson
Two Efforts Coming Together
IBEMC

• A collaborative working to:
  – Define the history and long-term clinical outcomes for IBEM ascertained by NBS and clinical identification
  – Permit development of evidence-based practice for patient care

• IBEMC developed a long-term follow-up tool “Inborn Errors of Metabolism-Information System” (IBEM-IS), a research platform
• Later joined efforts with NBSTRN to adapt and standardize the IBEM-IS
NBSTRN

• A NICHD contract was awarded to ACMG to develop tools and resources to support research in newborn screening (www.nbstrn.org)

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
History of the Inborn Errors of Metabolism – Information System (IBEM-IS)


- **2004-2007**: IBEM-IS was developed and implemented by the HRSA funded Region 4 LTFU Workgroup
  - 2007: Data entry began with MCAD deficiency

- **2007-2011**: IBEM-IS support continued through the HRSA funded Region 4 Priority 2 Project
  - Added new centers supported by other Regional Genetics Collaboratives (HRSA, NYMAC)

- **2011-present**: IBEM-IS support continued through the NIH funded Inborn Errors of Metabolism Collaborative (IBEMC)
  - 2013: Includes all IBEM on the Recommended Uniform Screening Panel
IBEMC Participants (2013)
23 Metabolic Centers in 16 States

Funding sources:
• NIH
• HRSA/MCHB Regional Newborn Screening and Genetics Collaboratives: New York-Mid-Atlantic, Heartland, and Region 4
IBEMC Case Enrollments
January 2009-January 2013

PKU/hyperphe  MCAD  AA'pathy  Galactosemia  Bio/HCS def  Other FAOD  OA

PKU/hyperphe  MCAD  AA'pathy  Galactosemia  Bio/HCS def  Other FAOD  OA
IBEMC Cases by Condition
January 2011-January 2013
# IBEMC Condition Count & NBS Ascertainment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Result</th>
<th>Count</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>3MCC</td>
<td>29</td>
<td>6</td>
<td>16</td>
<td>Mmahcy</td>
</tr>
<tr>
<td>3MGA</td>
<td>3</td>
<td>109</td>
<td>17</td>
<td>MMA</td>
</tr>
<tr>
<td>ASA</td>
<td>22</td>
<td>5</td>
<td>33</td>
<td>MSUD</td>
</tr>
<tr>
<td>Biopt</td>
<td>2</td>
<td>10</td>
<td>43</td>
<td>PROP</td>
</tr>
<tr>
<td>BTD</td>
<td>103</td>
<td>3</td>
<td>2</td>
<td>SBCAD</td>
</tr>
<tr>
<td>BKT</td>
<td>4</td>
<td>212</td>
<td>38</td>
<td>SCAD</td>
</tr>
<tr>
<td>CUD</td>
<td>16</td>
<td>7</td>
<td>10</td>
<td>TFP</td>
</tr>
<tr>
<td>Cit</td>
<td>10</td>
<td>26</td>
<td>9</td>
<td>Tyr</td>
</tr>
<tr>
<td>CPT1</td>
<td>2</td>
<td>18</td>
<td>56</td>
<td>VLCAD</td>
</tr>
<tr>
<td>CPT2</td>
<td>10</td>
<td>2</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>GA1</td>
<td>33</td>
<td>246</td>
<td>700/70%</td>
<td>#/ % by NBS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NBSTRN Research Pilots

- Identify collaborations that would benefit from NBSTRN infrastructure, resources and expertise
- Focus on needs of researchers and overarching goal of effort

- Current efforts
  - Natural history of newborn screened disorders
  - Novel technologies
  - Newborn screening pilots

- Future efforts
  - Genomic data
  - New conditions
  - Novel technologies
## Research Projects Utilizing NBSTRN

<table>
<thead>
<tr>
<th>Pilot</th>
<th>New Test</th>
<th>New Condition</th>
<th>New Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Combined Immune Deficiency</td>
<td><img src="204x192.png" alt="Image" /></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td><img src="300x201.png" alt="Image" /></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inborn Errors of Metabolism</td>
<td><img src="406x192.png" alt="Image" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysosomal Storage Disorders</td>
<td><img src="494x187.png" alt="Image" /></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
NBSTRN Tools

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
Key IBEMC-LPDR Components

**Objective**

- Enable investigators 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
Development

Review of Existing Data Sets
- IBEM-IS
- MSGRCC
- NYMAC
- NW Region/OHSU

Joint Committee Work
- Literature and key effort review
- Stakeholder engagement
- Use case development

Standards Alignment
- U.S. National Library of Medicine
- Eunice Kennedy Shriver National Institute of Child Health and Human Development
- National Institute of Neurological Disorders and Stroke
- Office of Rare Diseases Research
- American College of Medical Genetics
- Region 4 Stork

Longitudinal Pediatric Data Resource
- Case Report Forms
- REDCap™
- Data Almanac
  - sourced definitions, available at point of entry
  - Semantic definitions
  - LOINC, SNOMED

IBEM-IS
- LPDR Instance
- Feedback Survey
- Future Development

Data Sharing, Analysis & Dissemination

IBEMC Surveys

Review and Recommendation (R & R)

IBEM-IS Data Almanac (R & R)

LPDR pilot – real data, continuous R & R

Implementation, continuous R & R

Consent templates, MOU, SOP
Longitudinal Pediatric Data Resource (LPDR)

Common Data Elements (CDEs)
- Available
  - 46 RUSP
- 6 non-RUSP
  - SMA
  - LSDs
- In Process
  - 11 RUSP

Case Report Forms (CRFs)
- FISMA compliant
- Electronic and Printable
- 52 Conditions

Almanac & Analysis
- Definitions and standards
- Annotations
  - Genetics Home Reference
  - OMIM®
  - Human Gene Mutation Database®
- List of studies using same elements
- Analysis
  - Genomic data
  - Clinical data

Grantee Focus
- Inborn Errors Metabolism
  - >1400 cases
- Spinal Muscular Atrophy
  - Plan to screen 400,000 newborns
- Lysosomal Storage Disorders
  - Plan to screen 80,000 newborns

OA 33%
AA 30%
FAO 28%
New 12%
RUSP 88%
2013 Newborn Screening and Genetic Testing Symposium and International Society for Neonatal Screening

Attendees:
• Families
• Laboratory specialists
• Public health
• Clinicians
• Follow-up coordinators
• Informatics
• Educators
• NBS advocates
• Researchers
• Quality improvement/assurance specialists
• Many others

Consider the IBEMC-LPDR project possibilities and impact from your unique perspective...
### IBEMC Mock Case Example: Methylmalonic Acidemia (MUT)

<table>
<thead>
<tr>
<th>Intake Form</th>
<th>Visit Form</th>
<th>Independent Form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis: MMA MUT³</td>
<td>Insuranc: Medicaid</td>
<td>Language(s): English</td>
</tr>
<tr>
<td></td>
<td>Insurance: Medicaid</td>
<td>Medical Home: primary care</td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal complications: Sepsis, distress</td>
<td># Hospitalizations prior to Intake: 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic counseling: yes; provided by: GC</td>
<td>Comorbidities: anemia, short stature</td>
</tr>
<tr>
<td><strong>Health History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consanguinity</td>
<td>Sibling 1 affected: yes</td>
<td>Sibling 1 Method of diagnosis: Prenatal, molecular</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of dialysis episodes: 1</td>
<td>Dialysis type: CVVH</td>
<td>Peak ammonia: 1842 umol/L</td>
</tr>
<tr>
<td></td>
<td>Dialysis type: CVVH</td>
<td>Dialysis duration: 2 days</td>
</tr>
<tr>
<td><strong>Initial Testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBS: ↑C3, ↑24th tier MMA</td>
<td>Genotype, biochemical testing</td>
<td>Symptoms at time of initial metabolic contact: lethargy, failure to thrive, tachypnea, vomiting</td>
</tr>
<tr>
<td><strong>Visit Findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight: 17.4 kg</td>
<td>BP: 101/60</td>
<td>Exam findings: Evidence of hypotonia</td>
</tr>
<tr>
<td><strong>Visit Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labs</td>
<td>Home Monitoring</td>
<td>Imaging</td>
</tr>
<tr>
<td><strong>Visit Form</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy: levocarnitine 500 mg POTID, other</td>
<td>Nutrition: Metabolic formula, protein restricted diet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other management</td>
<td></td>
</tr>
<tr>
<td><strong>Ancillary Care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community resources: PCA, respite, social services</td>
<td>Developmental status: atypical, speech-language impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type of emergency contact information: letter, alert accessory</td>
<td></td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ: kidney</td>
<td>Reason: Renal failure</td>
<td>Procedure complications: metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>Metabolic labs post transplant: plasma amino acids, urine organic acids, plasma carnitine levels</td>
<td></td>
</tr>
</tbody>
</table>

### Demographics
- Date last specialty visit: 03/06/13
- Current insurance: Military
- Providers seen at this visit: Nurse Practitioner, dietitian, social worker, care coordinator

### Health History
- Immunizations: up to date
- Sick Visits: Reason: condition related, Location: ED, Admit: yes, # inpatient days: 5, # ICU days: 2
- Anesthesia since last visit: none

### Pregnancy
- # pregnancies = 0
- Complications: N/A
- Management: N/A
Current IBEMC Activity

• Pilot within Region 4 to export IBEMC data of interest to Public Health LTFU to NBS program
• Mapping IBEM-IS legacy data (DocSite™ to REDCap™), mostly a manual effort
• Reviewing and revising Data Almanac
• Pilot of LPDR eCRFs, pdf generator, Data Almanac in IBEM-IS instance completed
• Execution of Memorandum of Understanding between Michigan Public Health Institute and American College of Medical Genetics
IBEMC Accomplishments To Date

- As of 02/28/13: 1405 subjects consented (more than doubled since January 2012) with 31 different IBEM, 86 declined, 9 withdrawn (none due to study objection)
- IBEM-IS REDCap™ training materials developed, 24 clinicians/research coordinators trained
- IRB tools developed to address move from DocSite™ to REDCap™
- Standard Operating Procedures “Rules of Engagement”
- Established and initiated work of IBEM-IS research study teams currently focused on: VLCAD, MCAD, propionic acidemia, galactosemia, PKU, 3-MCC, general FAOD, & non-disorder specific issues
- IBEMC public website (www.ibem-is.org)
- IBEMC partner SharePoint site
- Monthly IBEMC conference calls (includes NBSTRN, HRSA, NIH)
- Cross-center data sharing for studies with results disseminated (publication, posters, platform presentations)
Example of IBEMC Project Findings: MCAD Deficiency (data collected from 2007-2013)

247 subjects with MCADD
- 202 by NBS (none deceased at the time of data analysis)
- 17 subjects diagnosed after clinical presentation (average age at data analysis 17.4y; 10 females 7 males)
- 170 NBS subjects had C8 values recorded (average age at data analysis 4.7y; 81 females 89 males)
  - 147 with at least one allele identified
  - 124 with at least one 985A>G mutation
  - Significant positive correlation between C8 values and the total number of 985A>G alleles (correlation coefficient = 0.43, p < 0.001)
- At the time of initial metabolic contact:
  - Average number of MCADD-related lab abnormalities in the high C8 group is significantly higher than that in the low C8 group (p=0.003)
  - Average number of MCADD-related symptoms in the high C8 group is significantly higher than that in the low C8 group (p=0.035)

Higher C8 values on NBS are more likely to be associated with lab abnormality, symptoms and homozygosity for the 985A>G mutation.
Newborns with higher NBS C8 values may benefit from even more rapid assessment/intervention.
IBEMC Next Steps

• **Revisit data sharing** with NBSTRN and revise data sharing plan if indicated
• Implement data sharing plan
• **Migration of legacy data** to NBSTRN LPDR according to IBEMC data sharing plan
• **Continue work of research study teams** and other research as opportunities present
• **Continue collaboration with NBSTRN**
• **Continuous quality improvement** of process, products and tools
NBSTRN Accomplishments to Date

• Secured authority from NIH to operate an information system that collects consented patient information (Federal Information Security Management Act/FISMA)

• Created a consensus-based set of common data elements (CDEs) available to the newborn screening community

• Developed a data almanac to provide definitions, annotations and links to other relevant resources

• Supporting grantees with active prospective longitudinal research projects focused in newborn screening
  – Metabolic Conditions
  – Spinal Muscular Atrophy
  – Lysosomal Storage Disorders
NBSTRN Future Work

• Continued Support of Existing Grantees
  – Grantee-supplied clinical data sharing, aggregation, analysis, case reporting and dissemination
  – Statistical support as needed

• Support of New Grantees
  – New conditions and technologies for LPDR development

• Genomics
  – Grantee-supplied genomic data
  – Analysis interface
Summary

• Standardization of consensus-based data sets for IBEM NBS conditions is possible and participation/use increases knowledge about IBEM, NBS and outcomes of affected individuals
• Assignment of codes is mostly a manual effort
• Understanding of clinical care workflows is key when designing data capture systems
• Centralized templates for standard operating procedures, consents and agreements facilitate initiation of grantee work
• Establishing a Federal information system is possible but requires expertise and resources
IBEMC Partnership

• Additional national and international partners are welcome and encouraged!

• Ethics Review Board/IRB review, approval and oversight are necessary: assistance with Federalwide Assurance, Authorization Agreement and obtaining IRB approval/oversight is available

• Agreement to comply with established Standard Operating Procedures developed by the IBEMC, revisited and modified as directed by our partners
NBSTRN Collaboration

www.nbstrn.org
Acknowledgments

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IBEMC Members and Contributors
• Susan A. Berry

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• Cynthia Cameron
• Sally Hiner
• Shaohui Zhai
• Kerie Hughes

Joint Committee
• NCC/RC LTFU Data Workgroup
• NBSTRN Clinical Centers Workgroup

NBSTRN
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• Amy Brower
• Amy Hoffman
• Bruce Bowdish

CHOP
• Jen Loutrel
• Stacey Wrazien
• Peter White
• Jeff Pennington
• Mark Porter

Family Participants
Thank You!

www.ibem-is.org

www.nbstrn.org