The Inborn Errors of Metabolism Collaborative (IBEMC) – an Update

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Why LTFU?

“Newborn screening is more than testing. It is a coordinated and comprehensive system consisting of education, screening, follow-up, diagnosis, treatment and management, and program evaluation.”

*Newborn Screening: Toward a Uniform Screening Panel and System*
Long-Term Follow-Up in Context

First 6 Months

Next 80 (or more) Years

(not drawn to scale!!)
Where we started in Region 4: Try a treatment and follow-up protocol? Could not...

- Reviewed treatment plans contributed by all partners; data sets from others
- Identified elements that all agree are essential and that should be done uniformly
- Identified elements that are anecdotal and could be subject to randomization
Research as a fundamental assumption

• Data collection plans initiated with selected research questions in mind
• Hypotheses are implied by the elements collected (are also generated subsequently)
• “Natural” history isn’t natural
IBEM-IS: developing a larger scale follow-up record as a platform for research; a model for a national platform

• Started with one disorder (MCAD deficiency)
  – Developed demographic database
  – Developed condition-specific data elements
• Defined issues for short- and long-term f/u
• Agreed about how to add additional disorders
• Planned together to have accessible information that is easy to maintain
• Documenting consent to allow continuing contact, anticipating engaging subjects as participants in future research trials
History of the Inborn Errors of Metabolism – Information System (IBEM-IS)


2004-2007
IBEM-IS 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 (Heartland, 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
About the NBSTRN

• The NBSTRN is an NICHD-funded contract, awarded to ACMG in September 2013 until September 2018

• The NBSTRN will maintain, administer and enhance resources to support investigators with projects related to newborn screening for:
  – New technologies
  – New conditions
  – New treatments and management approaches
<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>VRDBS</td>
<td>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.</td>
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<tr>
<td>LPDR</td>
<td>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.</td>
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<tr>
<td>R4S</td>
<td>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.</td>
</tr>
</tbody>
</table>
The Joint Committee: Lots of cooperation! (for lots and lots of data elements...)
Long-term follow-up, IBEMC, and the NBSTRN-LPDR

**IBEMC Goals**

- Improve knowledge about the clinical history of persons with IBEM on a long-term basis
- Gather evidence about effective management and treatment strategies for persons with IBEM

*IBEMC is an NIH grantee collaborating on tool-generation for the LPDR*
IBEMC Methods

- Elements from treatment protocols, other data sets, literature review – practice style differences captured (not prescribed)
- *Prospective informed consent*
- Ascertainment at clinic visits or via mail
- Sample of convenience – depends on who says yes and patients attending
- Data gathered using web-based, password protected data entry forms
### Conditions with Data Collection Tools

#### Core Conditions
- **Aminoacidopathies**
  - Phenylketonuria (classical)
  - MSUD
  - Homocystinuria
  - Tyrosinemia type I
  - Argininosuccinic acidemia
  - Citrullinemia type I

- **FAOD**
  - MCAD deficiency
  - VLCAD deficiency
  - LCHAD deficiency
  - TFP deficiency
  - Carnitine uptake defect

- **OAs**
  - Isovaleric acidemia
  - Glutaric acidemia type I
  - HMG deficiency
  - 3MCC deficiency
  - BKT deficiency
  - Multiple carboxylase deficiency
  - Methylmalonic acidemia (MUT)
  - Methylmalonic acidemia (Cbl A,B)
  - Propionic acidemia

- **Other**
  - Biotinidase deficiency
  - Galactosemia

#### Secondary Conditions
- **Aminoacidopathies**
  - Hyperphenylalaninemia
  - Tyrosinemia type II
  - Tyrosinemia type III
  - Biopterin defects (Bios)
  - Biopterin (Reg)
  - Argininemia
  - Hypermethioninemia
  - Citrullinemia type II

- **FAOD**
  - M/SCHAD deficiency
  - SCAD deficiency
  - MCKAT deficiency
  - CPT-I deficiency
  - CPT-II deficiency
  - Glutaric acidemia type II
  - CACT deficiency
  - 2,4 Dienoyl reductase deficiency

- **OAs**
  - Methylmalonic acidemia (Cbl C,D)
  - 2M3HBA deficiency
  - IBG deficiency
  - 2MBCAD deficiency
  - 3-Methylglutaconic aciduria

- **Other**
  - Malonic acidemia
  - Biotinidase deficiency
  - Galactosemia
  - GalE, GalK
By disorder

(since REDCap data entry started)
Subject Characteristics as of 8/20/14

1698 total subjects with demographics entered
Age range: < 1 mo to 62 yr (289 age 18 y or over)
  Average 11.01 yr, median age 8 yr
Gender distribution: M - 885; F - 813
Racial distribution (1412 with any answer)
  African American/Black – 77
  Asian – 11
  Hispanic/Latino – 49
  Native American/Alaska Native – 2
  Multiracial – 40
  Other – 19
  Unknown/not specified/not reported – 81
  Declined – 1
  White – 1132
## Data: Numbers and Contacts

<table>
<thead>
<tr>
<th>Query</th>
<th># With finding</th>
<th>Total with data</th>
<th>% of Total</th>
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<tbody>
<tr>
<td>Agree to re-contact</td>
<td></td>
<td>941</td>
<td></td>
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<tr>
<td>Yes</td>
<td>759</td>
<td></td>
<td>81%</td>
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<tr>
<td>No</td>
<td>182</td>
<td></td>
<td>19%</td>
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<tr>
<td>Diagnosis by</td>
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<tr>
<td>NBS</td>
<td>1096</td>
<td></td>
<td>82%</td>
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<tr>
<td>Family member</td>
<td>74</td>
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<td>6%</td>
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<tr>
<td>Clinical</td>
<td>152</td>
<td></td>
<td>11%</td>
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<tr>
<td>Lab</td>
<td>19</td>
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<tr>
<td>Genetic counseling</td>
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<td>1304</td>
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<tr>
<td>Yes</td>
<td>1175</td>
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<td>90%</td>
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<tr>
<td>No</td>
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<td></td>
<td>4%</td>
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<tr>
<td>Unk</td>
<td>79</td>
<td></td>
<td>6%</td>
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1435 with data in the requested data set

1085 were identified by NBS

771 with “days from birth to intervention for this IBEM” as a completed data element

• Average for ALL disorders: 20.5 days
• Average for critical (SIMD) disorders: 12.4 days
• Average for non-critical disorders: 30 days
Early complications of MCAD deficiency

- Assess the impact of C8 value
- Assess the impact of genotype

(presentation for ACMG – Mar 2013)
Elements abstracted for analysis

- If deceased, date of death
- Mutation description: Allele 1, Allele 2
- C8 on first NBS
- Lab abnormalities at time patient or primary care provider (on behalf of patient) first contacts metabolic specialist (*multichack box+“other”*)
- Symptom(s) at time of initial metabolic contact (*multichack box+“other”*)
- Initial diagnosis of this IBEM found by: (*multichack box*)
Subject characteristics

• 247 total subjects with MCADD ascertained
• 202 subjects diagnosed by NBS
  – No subjects diagnosed by NBS had died
• 17 subjects diagnosed by clinical presentation (average age 17.4y; 10F 7M)
• 170 NBS subjects had C8 values recorded (average age 4.7y; 81F 89M)
  – 147 with at least one allele identified
  – 124 with at least one 985A>G
C8 values on NBS (μmol/L)
MCADD-related Symptoms or Labs

Number of events

- Low Quarter
- High Quarter

MCAD related lab

MCAD related symptom
Number of 985A>G alleles

Low Quarter

High Quarter

Number of subjects

0 5 10 15 20 25 30

other/other 985/other 985/985

- Low Quarter
- High Quarter

Inborn Errors of Metabolism Collaborative
Conclusions

• Higher C8 values found on NBS are more likely to be associated with lab abnormality, symptoms and homozygosity for 985A>G

• Infants with high C8 values are more likely to have clinically concerning symptoms or lab values

We suggest extra precautions in assessment of infants with higher C8-acylcarnitine values on NBS
Where are we now, what next?

• New accomplishment via IBEMC collaboration with NBSTRN
  – Using REDCap web-based data collection (“instance” at MPHI)
• Added condition-specific research programs

  NEXT:
• Continue enrollment, data collection
• Add new participating centers
• Collaboration with other research projects
• Add specific research surveys
• Enable public health leaders to make informed decisions about optimal investment in NBS
• Publish initial findings from largest data sets
IBEMC public website:

www.ibem-is.org
IBEMC Participants (2014)
27 Metabolic Centers in 20 States

Funding sources:
- NIH
- HRSA/MCHB Regional Newborn Screening and Genetics Collaboratives:
  - New York-Mid-Atlantic, Heartland,
  - Mountain States and Region 4 (Midwest)
## Acknowledgements

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<thead>
<tr>
<th>Clinic</th>
<th>Clinician</th>
<th>Res. Coordinator</th>
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<tbody>
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<td>Arkansas Children’s Hospital</td>
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<td>Children’s Hospital Colorado</td>
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<td>Erica Wright</td>
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<td>Sue Lipinski</td>
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<td>*University of Pittsburgh</td>
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