Inborn Errors of Metabolism Collaborative: Long-Term Follow-Up to Develop Evidence-Based Newborn Screening and Management Strategies for Inborn Errors of Metabolism

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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!!)

NCC
National Coordinating Center
for the Regional Genetic Service Collaboratives
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
Switch to RedCap for data collection
NBSTRN Research 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.
The Joint Committee: Lots of cooperation! (for lots and lots of data elements...)

- LTFU Committee
- LPDR
- Clinical Centers Workgroup

NCC
National Coordinating Center
for the Regional Genetic Service Collaboratives

NBSTRN
Newborn Screening Translational Research Network

IBEMC
Inborn Errors of Metabolism Collaborative

ACMG
Long-term follow-up, IBEMC, and the NBSTRN-LPDR

**IBEMC Goals – first 5 years**

- 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
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
 Methylnalonic acidemia (MUT)
 Methylnalonic 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
 Methylnalonic acidemia (Cbl C,D)
 2M3HBA deficiency
 IBG deficiency
 2MBCAD deficiency
 3-Methylglutaconic aciduria
 Malonic acidemia
   Other
 GalE, GalK
Cases as of Aug 2015
Scope of Data Collection

Inputs
- Researchers & Clinicians
- Families

Resources
- IBEM-IS LPDR
- Data Collection, Organization, & Storage
  - 7,299 Unique Data Elements
  - 544,838 Completed Data Fields

Outputs
- Patient Demographics
  - 3,040 Data Elements
- Special Situations (pregnancy, transplant)
  - 1,744 Data Elements
- Longitudinal Clinical Data
  - 2,515 Data Elements
IBEM-IS and LPDR

• NBSTRN as support and facilitator of NBS research: Collaboration in tool generation

• Data use agreement mutually needed for clear understanding about data use and responsibilities

• **SIGNED, SEALED, DELIVERED – data transfer from IBEM-IS to LPDR in process**
Where are we now, what next?

• Via IBEMC collaboration with NBSTRN now using REDCap web-based data collection (“instance” at MPHI)
• Added condition-specific research program
• Continue enrollment, data collection
• Adding new participating centers

Next:
• Collaboration with other research projects
• Enable public health leaders to make informed decisions about optimal investment in NBS
• Publish initial findings from largest data sets
• PPG for continuing funding
Example: PKU Project

Rationale: Characterize the status of our cohort

- Gender, ethnicity, age of patient at diagnosis,
- Diagnosed by newborn screening (yes/no)
- Blood phenylalanine level at diagnosis;
- Age at treatment start
- On dietary treatment (yes/no)
- Ever treated with sapropterin (yes/no)
- Currently treated with sapropterin (yes/no)
- Ever treated with LNAA (yes/no);
- Genotype available?
  - if so, what are they?
- Current weight percentile for age
- Current height percentile for age
Forms used for data collection: PKU

PKU_dialysis
PKU_intake_demographics
PKU_intake_family_history
PKU_intake_initial_testing
PKU_intake_newborn_screening
PKU_intake_past_health_history
PKU_pregnancy
PKU_transplant
PKU_visit_ancillary_care
PKU_visit_demographics_and_history
PKU_visit_findings
PKU_visit_health_history
PKU_visit_lab_studies
PKU_visit_management_and_treatment_nutrition
PKU_visit_management_and_treatment_pharmacotherapy
**REDCap Event Grid**

*73-17* is a new IBEM-IS ID. You will need to click any of the red buttons below to create a record for this IBEM-IS ID and begin entering data for it.

The grid below displays the form-by-form progress of data entered into the project for one particular IBEM-IS ID for all defined events. You may click on the colored buttons to access that form for that event. If you wish, you may modify the events below by navigating to the Define My Events page.

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<th>Data Collection Instrument</th>
<th>Intake</th>
<th>Visit 1</th>
<th>Other</th>
<th>Visit 2</th>
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<th>Visit 4</th>
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Example: Intake
Example: Visit

### Visit Management And Treatment Nutrition

**Event Name:** Visit 1  
**IBEM-IS ID:** 73-17

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<tbody>
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<tr>
<td>Oral</td>
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<tr>
<td>NG tube</td>
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<tr>
<td>NJ tube</td>
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<tr>
<td>G-tube</td>
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<td>GJ tube</td>
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<td>TPN</td>
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<th>Mode of nutrition delivery</th>
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<tr>
<td>None</td>
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<tr>
<td>Baby formula (regular)</td>
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<td>Baby formula (soy)</td>
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<td>Elemental formula</td>
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<tr>
<td>Breast milk</td>
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<tr>
<td>Human milk fortifier</td>
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<td>Almond milk</td>
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<td>Rice milk</td>
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<td>Soy milk</td>
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<td>Special metabolic formula</td>
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<td>Toddler formula (regular)</td>
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<td>Toddler formula (soy)</td>
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<td>Whole milk</td>
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<thead>
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<th>Types of milk/formula taken</th>
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<td>Protein restricted diet recommended/prescribed</td>
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Amount of protein grams recommended/prescribed from food per day (not including metabolic formula) for protein restricted diet
Program Project Grant Proposal

Synergy Among Projects and Outcomes

Project 1
Clinical history & management

Project 2
Psychosocial history & management

Project 3
Clinical & Psychosocial history & management

Health, cognitive, behavioral, and emotional outcomes for clinical and subclinical conditions

Evidence for clinical & neuropsychological practice

Evidence for newborn screening & long term follow-up policy

Patients achieve full potential for healthy and productive lives
Our plan

Project 1:
Clinical management and treatment practices; develop strategies for optimizing long term outcomes

Family Core:
Provide evidence relevant and responsive to patient needs

Re-sequencing Core:
Evaluate the feasibility and accuracy of using genetic data in screening for IBEM

Admin Core:
Convene and administer the Program Project

Data Core:
Cost-effective data collection, management, & analysis

Project 2:
Neurocognitive, behavioral, & emotional consequences of IBEM; develop strategies for optimizing long term outcomes

Project 3:
Clinical management and treatment practices for subclinical IBEM; develop strategies for improved ascertainment and follow-up
Hypothesis: By examining current management and treatment practices, optimal strategies for improving outcomes can be elucidated.

Project 1:

1. Determine the impact on clinical outcomes of interventions for individuals with newborn-screened conditions.
2. Determine the relationship between newborn screening values and acuity of condition.
Hypothesis: By assessing the neurocognitive, behavioral and emotional consequences of NBS conditions and considering these factors in relation to medical and genetic information, we can develop strategies for optimizing long-term outcomes for those with IBEMs and their families.

1. Clarify disease definitions in newborn screened metabolic disorders with respect to long-term neurocognitive, behavioral, and emotional outcomes
2. Identify barriers to optimal Quality of Life (QoL) for participants with IBEMs and their families.
3. Formulate an evidence-based plan for neuropsychological, behavioral, and emotional follow-up of persons with newborn-screened IBEMs that optimizes long-term outcomes and a positive quality of life.
Hypothesis: By examining current management practices and outcomes for patients with subclinical conditions, optimal strategies for improving ascertainment and follow-up of individuals with these conditions will be elucidated.

1. Engage families in a sustainable longitudinal data collection process that is independent of clinic preferences for follow-up
2. Assess health and developmental outcomes for individuals with subclinical conditions
3. Utilize the patient-reported outcomes generated (scientific evidence generated) to impact practice and policy throughout the newborn screening system.
Re-sequencing Core Details

Objectives:
Evaluate the feasibility and accuracy of using genetic data in screening for IBEM

1. Generate high-quality sequence data covering genes relevant to IBEM detected by tandem mass spectrometry.
2. Provide genotype data on subjects diagnosed with IBEM through newborn screening.
3. Determine the sensitivity and specificity of genetic variant analysis for the prediction of affected status for IBEM.
Family Core Details

Objectives:
To ensure the research projects provide evidence relevant and responsive to patient needs.

1. Launch the IBEMC Family Network
2. Ensure integration of the patient/family voice with the research projects
3. Guide the research process through a broad perspective of the concerns and issues of families and patients
4. Disseminate research findings and promote translation of evidence to clinical and public health practice
Our goal: creating an evidence base to improve outcomes

Hypothesis:
By examining current management and treatment practices, optimal strategies for improving outcomes can be elucidated.

Hypothesis:
By assessing the neurocognitive, behavioral and emotional consequences of NBS conditions and considering these factors in relation to medical and genetic information, we can develop strategies for optimizing long-term outcomes for those with IBEMs and their families.

Hypothesis:
By examining current management practices and outcomes for patients with subclinical conditions, optimal strategies for improving ascertainment and follow-up of individuals with these conditions will be elucidated.
IBEMC public website:
www.ibem-is.org
IBEMC Participants (2015)
30 Metabolic Centers in 21 States

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

• Cynthia Cameron – Co PI
• Sally Hiner – Project Coordinator
• Mat Edick – Project Scientist
• MPHI Staff
• ALL SITES!!

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Region 4(Midwest), NYMAC, Heartland, Mountain States

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