Long-Term Follow-Up after Newborn Bloodspot Screening: Why, How, and What Next?

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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

Expanded NBS: a national priority

- Justice - all should be screened equally
- NBS should improve outcomes and save lives
- NBS is only as effective as the care it prompts
- Collaboration between screening, short term, and long term team members is critical to improved outcomes
- Data sharing is essential

What did we want to do? Challenges presented in doing trials for treatment in IBEM

- Clinicians realized we all had experience but little evidence
- All the conditions are rare, even the "common" ones
- Conditions affect children
- Hard to justify testing accepted treatments that seem to work
- Who will pay?

Our original proposal: select a condition and treat using a uniform protocol

- Suggested disorder: MCAD
- Incidence 1:10600 (MN) so ~ 70/yr in Region4
- Therapy critical element agreed upon (prevention of fasting)
- Other elements of treatment plan anecdotal
  - Carnitine?
  - Cornstarch?
  - Diet modification?

Strategies for developing an evidence base for management in IBEM

- Collaboration between centers
- Federal and state support to encourage
- Teaching principles of EBM in clinical genetics training
- Improving precision of terminology so published reports are accessed in appropriate searches
- Publication of systematic reviews of IBE management

(adapted from Steiner: Amer J Med Genet 134A:192, 2005)

How? One group's efforts

- Region 4 Genetics Collaborative LTFU
- Region 4 HRSA Priority 2 Workgroup (R4P2)
- Inborn Errors of Metabolism Collaborative

These are all (the same, gradually enlarging) group of clinicians who want to save lives and improve outcomes for persons affected with NBS-screened conditions

The early evolution: Region 4 MCADD Registry

- Initiating a uniform treatment protocol: great concept, very difficult to pull off
- No “natural” history defined for assessment of outcomes when new treatments/protocols are applied
- Lots of clinicians, lots of successful strategies

Summary: gathering uniform data and assessing clinical practice differences is a way to learn which treatment strategies are most effective

Region4
Genetics Collaborative

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

Region4
Genetics Collaborative

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*

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Enrollment Data Elements

Demographics (common to all disorders)

- Unique Registry ID Number
- *Patient name
- *Date of birth
- *State newborn screen serial number
- Is patient followed by more than one metabolic center?
- Gender
- Race of patient
- Special ethnic group
- Birth weight
- Birth length
- OFC
- Maternal educational level
- Paternal educational level
- Affected siblings?

Presentation: (includes disease-specific data)

- Pregnancy History
- Means of initial diagnosis
- Days of age at time family was notified of diagnosis
- Days of age at time abnormal screen reported to primary provider:
- Days of age at time abnormal newborn reported to metabolic provider:
- Days of age from birth to physician notification of abnormal screen result:
- Days of age from birth to treatment:
- Days of age at time of initial newborn screen collection:
- Days of age at time of initial face to face metabolic consultation with family

Enrollment Data Elements - II

Presentation (cont.)

- Method of diagnosis
- Analyte levels on newborn screen
- Symptoms and laboratory findings present at initial metabolic consultation
- Was prenatal testing done during this pregnancy?
- Diagnostic tests obtained
- Confirmatory tests
- Genotype

Initial Care Plans:

- Genetic counseling was provided
- Family was given a written emergency medical alert plan
- Family was given 24-hour on-call contact for metabolic provider
- Patient was enrolled in a web-based emergency medical alert plan
- Internet/written support information was provided

Interval Elements

Follow up Status

- Is the patient still alive?
- Date of death OR Date of last contact
- Cause of death
- Weight
- Height
- OFC

Laboratory testing

- Laboratory tests collected
- Imaging tests performed

Emergency care/hospitalizations

- Number of emergency visits since the last metabolic visit
  - metabolic related
- Number of hospital admissions since last metabolic visit
  - metabolic related hospital days
- (Disorder-specific complications)
- (Disorder-specific monitoring used)
- Patient has a sick day plan

Interval Elements - II

- *Developmental evaluation*
- Developmental milestones achieved
- If no, which developmental milestones not achieved
- Patient referred for further evaluation?
- Are behavioral concerns suspected?
- If yes patient was referred for further evaluation?
- Referral for Special Education evaluation?
- Neuropsychological assessment completed since the last metabolic visit?
- Educational Services Currently received

Care coordination

- Current insurance coverage:
- Community referrals
- Health care referrals

Pharmacotherapy

- (disorder specific medication prescribed)
- Family reports compliance with medication

Nutrition intervention

- (disorder specific nutritional intervention)
- Family reports compliance with nutrition intervention

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

Berry SA, Jurek AM, Anderson C, Bentler K; Region 4 Genetics Collaborative Priority 2 Workgroup. The inborn errors of metabolism information system: A project of the Region 4 Genetics Collaborative Priority 2 Workgroup. Genet Med. 2010 Dec;12(12 Suppl):S215-9.

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

The Joint Committee: Lots of cooperation! (for lots and lots of data elements…)

LTFU Committee

LPDR
Longitudinal
Pediatric
Data
Resource

Clinical Centers Workgroup

ACMG

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

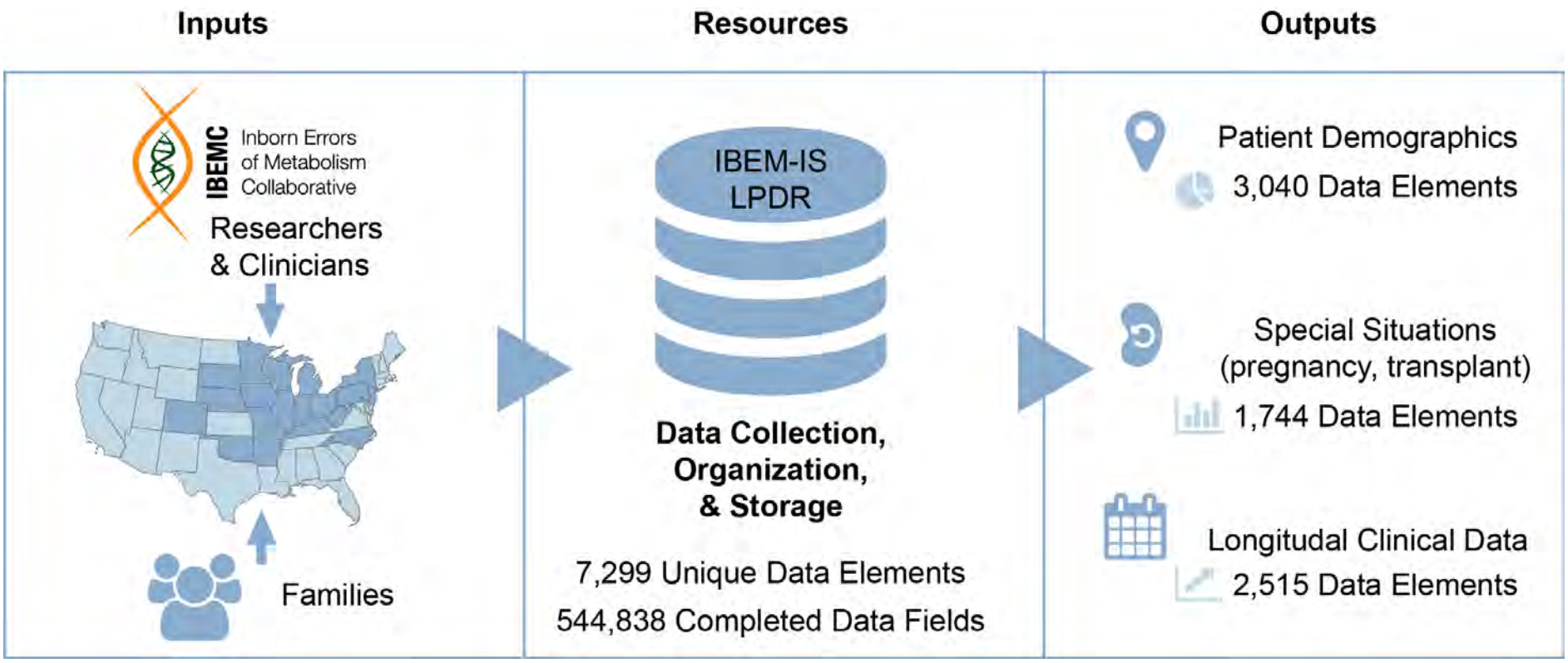
IBEMC is an NIH grantee collaborating on tool-generation for the LPDR

ACMG

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

Scope of Data Collection



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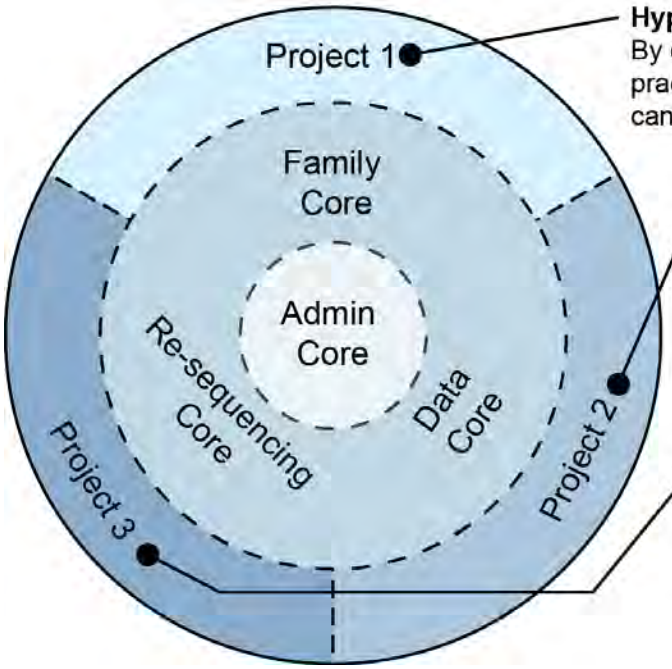
Our goal: creating an evidence base to improve outcomes



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.

Improved Outcomes

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IBEMC public website:

https://www.ibem-is.org/

New variations on older paradigms for inclusion on NBS

Original intent:

- Include conditions with demonstrable impacts of early treatment
  - Some yes, some no for our new ones
  - (but then some old ones didn't either…)
- Add conditions with effective treatments
  - Some yes, some no for the new ones
  - (but then some old ones, not so much either)

What is different with the newly added conditions?

- Timing of therapies
- Effectiveness of therapies
- Cost of therapies
- Timing of onset of manifestations of the conditions

The big difference?

Impact of adult-onset variations of these conditions

(and the corollary, timing for interventions)

Implications:
Where do we go from here?

- Conditions added with late-onset and poorly characterized long-term interventions
- Limited knowledge of timing and utility of early interventions
- No current infrastructure for LTFU after Dx
- [Conditions added by legislative mandate without evidence review]

Advances in knowledge
Balance: general and individual

- Public Health research – responsibilities to populations and the general good
- Individual persons identified by screening – responsibilities to improve outcomes for each person found

Final Implications

- We have signed up for a bigger, more permanent job (but we always had it, BTW)
- Keeping up with persons identified with late-onset disorders will require new, complex infrastructure – no matter where it lives
- We OWE the families and ourselves advancements in knowledge from follow-up and new treatment initiatives

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