



# 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**

Inborn Errors  
of Metabolism  
Collaborative



N B S T R N

NEWBORN  
SCREENING  
TRANSLATIONAL  
RESEARCH  
NETWORK

# IBEMC

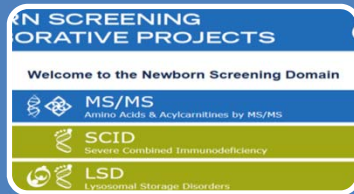


- A collaborative working to:
  - Define the history and long-term clinical outcomes for IBEM ascertained by NBS and clinical identification
  - Permit development of evidence-based practice for patient care
- IBEMC developed a long-term follow-up tool “Inborn Errors of Metabolism-Information System” (IBEM-IS), a research platform
- Later joined efforts with NBSTRN to adapt and standardize the IBEM-IS

# NBSTRN

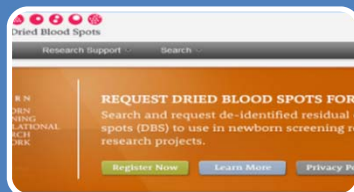


- A NICHD contract was awarded to ACMG to develop tools and resources to support research in newborn screening ([www.nbstrn.org](http://www.nbstrn.org))



## 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)

*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 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**

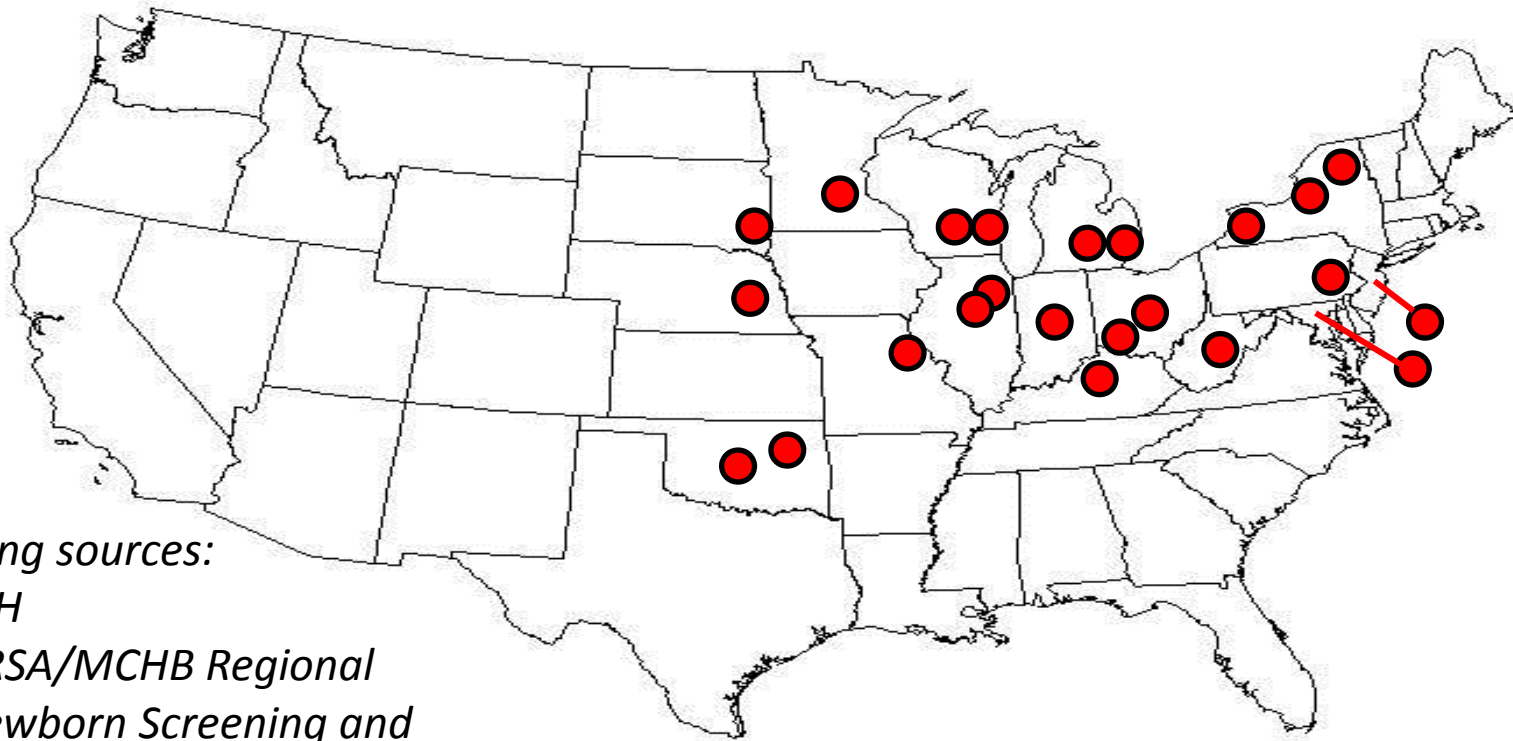
**IBEM-IS support continued through the NIH funded Inborn Errors of Metabolism Collaborative (IBEMC)**

2013: Includes all IBEM on the Recommended Uniform Screening Panel



# IBEMC Participants (2013)

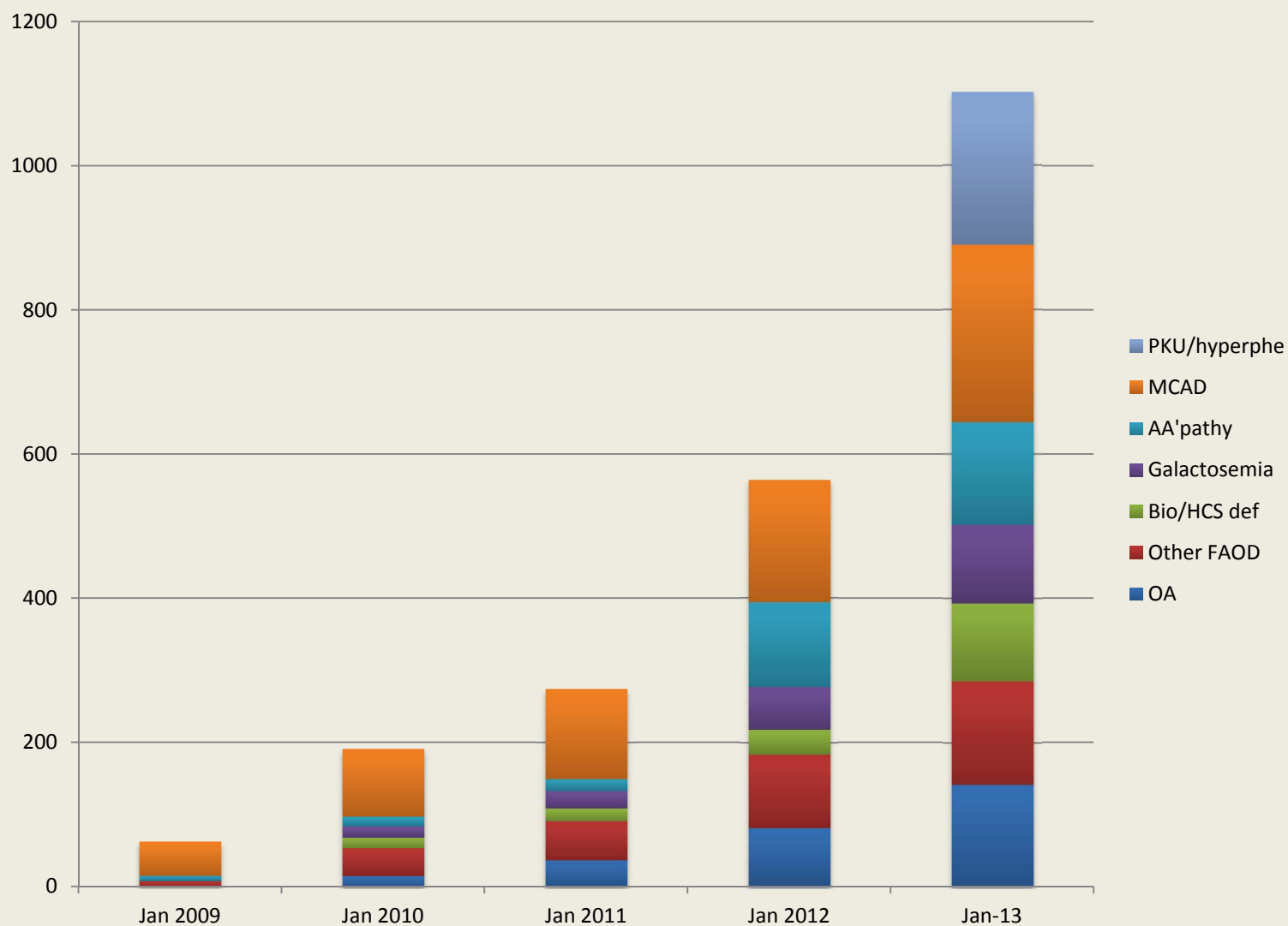
## 23 Metabolic Centers in 16 States



### *Funding sources:*

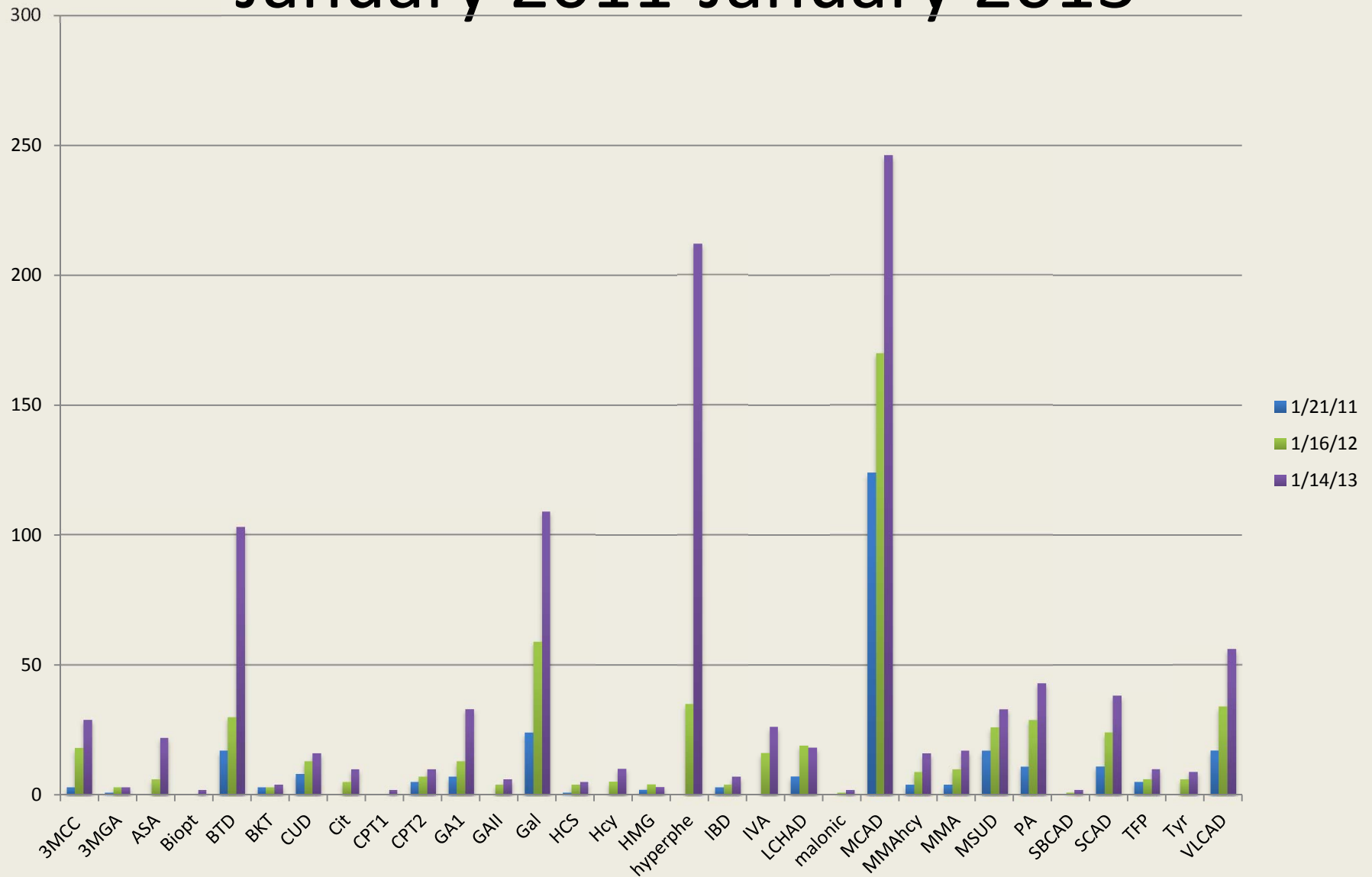
- *NIH*
- *HRSA/MCHB Regional Newborn Screening and Genetics Collaboratives: New York-Mid-Atlantic, Heartland, and Region 4*

# IBEMC Case Enrollments January 2009-January 2013



# IBEMC Cases by Condition

## January 2011-January 2013











# IBEMC Condition Count & NBS Ascertainment

3MCC	29		GAI	6		Mmahcy	16
3MGA	3		Gal	109		MMA	17
ASA	22		HCS	5		MSUD	33
Biopt	2		Hcy	10		PROP	43
BTD	103		HMG	3		SBCAD	2
BKT	4		HyperphePK U	212		SCAD	38
CUD	16		IBD	7		TFP	10
Cit	10		IVA	26		Tyr	9
CPT1	2		LCHAD	18		VLCAD	56
CPT2	10		malonic	2		Total	1102
GA1	33		MCAD	246		#/% by NBS	700/70%

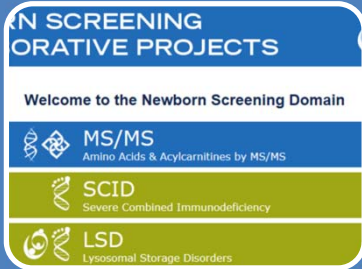
# NBSTRN Research Pilots

- 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

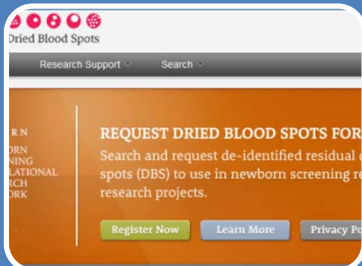
Pilot		New Test	New Condition	New Treatment
Severe Combined Immune Deficiency		✓	✓	
Spinal Muscular Atrophy		✓	✓	✓
Inborn Errors of Metabolism				✓
Lysosomal Storage Disorders		✓	✓	✓

# 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

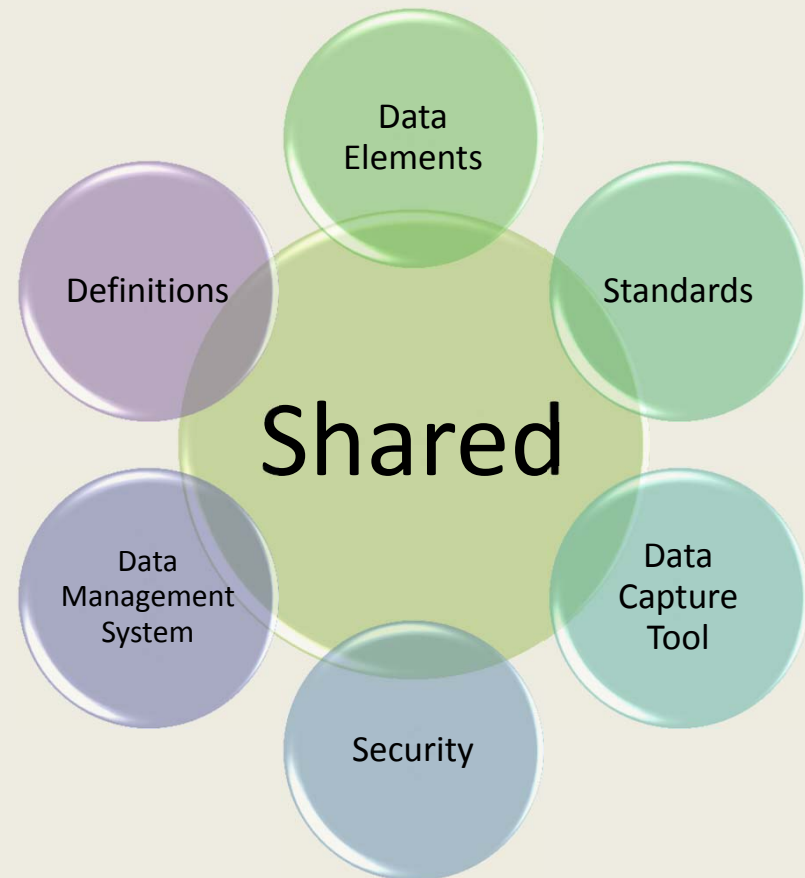
# Key IBEMC-LPDR Components

## 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

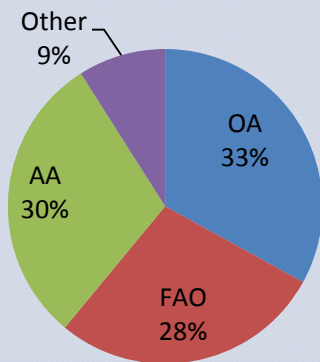
Implementation, continuous R & R

Consent templates, MOU, SOP

# Longitudinal Pediatric Data Resource (LPDR)

## Common Data Elements (CDEs)

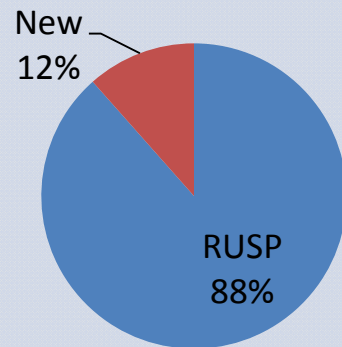
- Available
  - 46 RUSP



- 6 non-RUSP
  - SMA
  - LSDs
- In Process
  - 11 RUSP

## Case Report Forms (CRFs)

- FISMA compliant
- Electronic and Printable
- 52 Conditions



- 17 Categories

## 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

# 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

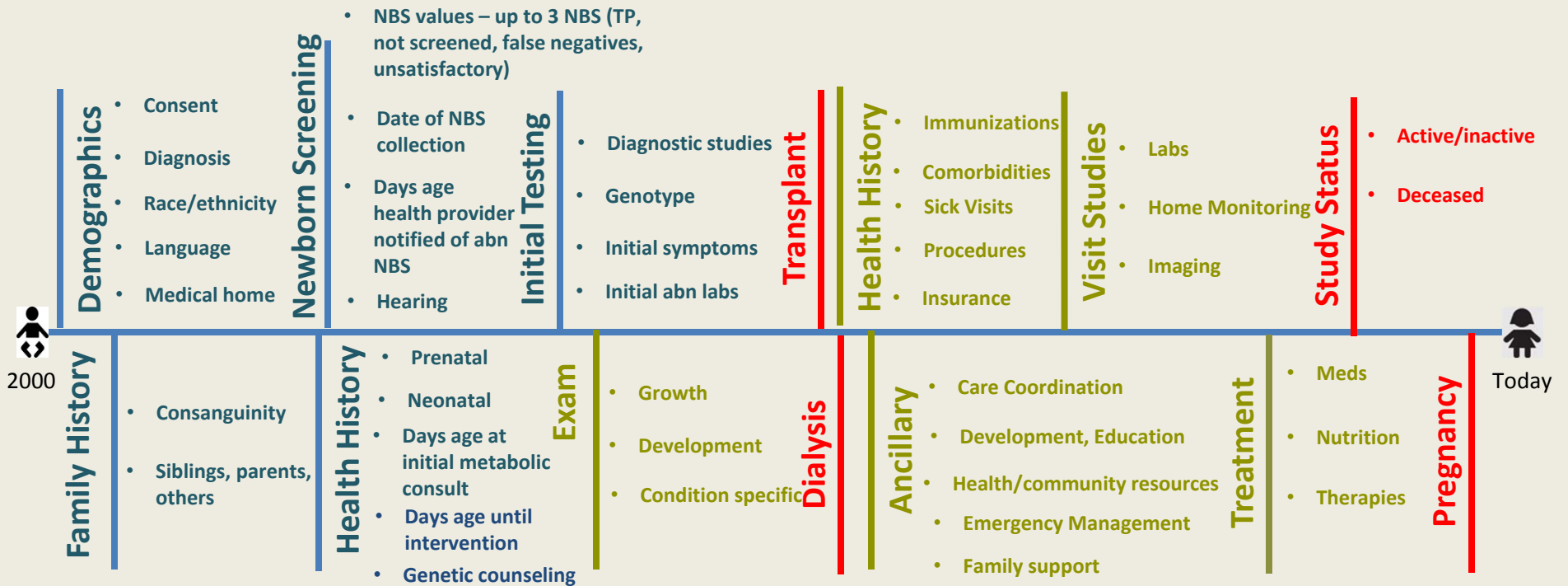
**Consider the IBEMC-LPDR project possibilities and impact from your unique perspective...**



# LPDR Case Report Forms


Subject | Longitudinal Care Record

- Intake
- Every Visit
- Study Status, Pregnancy, Dialysis, Transplant



# IBEMC Mock Case Example: Methylmalonic Acidemia (MUT)

- Intake Form
- Visit Form
- Independent Form

	<b>Demographics</b>	<ul style="list-style-type: none"> <li>• Diagnosis: MMA MUT<sup>o</sup></li> <li>• Insurance: Medicaid</li> <li>• Language(s): English</li> <li>• Medical Home: primary care</li> </ul>	<b>Study Status</b>	<ul style="list-style-type: none"> <li>• Active</li> </ul>	<b>Health History</b>	<ul style="list-style-type: none"> <li>• Neonatal complications: Sepsis, distress</li> <li>• # Hospitalizations prior to intake: 7</li> <li>• Genetic counseling: yes; provided by: GC</li> <li>• Comorbidities: anemia, short stature</li> </ul>	<b>Demographics</b>	<ul style="list-style-type: none"> <li>• Date last specialty visit: 03/06/13</li> <li>• Current insurance: Military</li> <li>• Providers seen at this visit: Nurse Practitioner, dietitian, social worker, care coordinator</li> </ul>
	<b>Dialysis</b>	<ul style="list-style-type: none"> <li>• # of dialysis episodes: 1</li> <li>• Dialysis type: CVVD</li> <li>• Peak ammonia: 1842 umol/L</li> <li>• Dialysis duration: 2 days</li> </ul>	<b>Initial Testing</b>	<ul style="list-style-type: none"> <li>• NBS: ↑C3, ↑2<sup>nd</sup> tier MMA</li> <li>• Genotype, biochemical testing</li> <li>• Symptoms at time of initial metabolic contact: lethargy, failure to thrive, tachypnea, vomiting</li> </ul>	<b>Family History</b>	<ul style="list-style-type: none"> <li>• Consanguinity</li> <li>• Sibling 1 affected: yes</li> <li>• Sibling 1 Method of diagnosis: Prenatal, molecular</li> </ul>	<b>Health History</b>	<ul style="list-style-type: none"> <li>• Immunizations: up to date</li> <li>• Sick Visits: Reason: condition related, Location: ED, Admit: yes, # inpatient days: 6, # ICU days: 2</li> <li>• Anesthesia since last visit: none</li> </ul>
	<b>Visit Findings</b>	<ul style="list-style-type: none"> <li>• Weight: 17.4 kg</li> <li>• BP: 101/60</li> <li>• Exam findings: Evidence of hypotonia</li> </ul>	<b>Visit Studies</b>	<ul style="list-style-type: none"> <li>• Labs</li> <li>• Home Monitoring</li> <li>• Imaging</li> </ul>	<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Pharmacotherapy: levocarnitine 500 mg PO TID, other</li> <li>• Nutrition: Metabolic formula, protein restricted diet</li> <li>• Other management</li> </ul>	<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• # pregnancies = 0</li> <li>• Complications: N/A</li> <li>• Management: N/A</li> </ul>
	<b>Ancillary Care</b>	<ul style="list-style-type: none"> <li>• Community resources: PCA, respite, social services</li> <li>• Developmental status: atypical, speech-language impairment</li> <li>• Type of emergency contact information: letter, alert accessory</li> </ul>	<b>Transplant</b>	<ul style="list-style-type: none"> <li>• Organ: kidney</li> <li>• Reason: Renal failure</li> <li>• Procedure complications: metabolic acidosis</li> <li>• Metabolic labs post transplant: plasma amino acids, urine organic acids, plasma carnitine levels</li> </ul>				

# 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

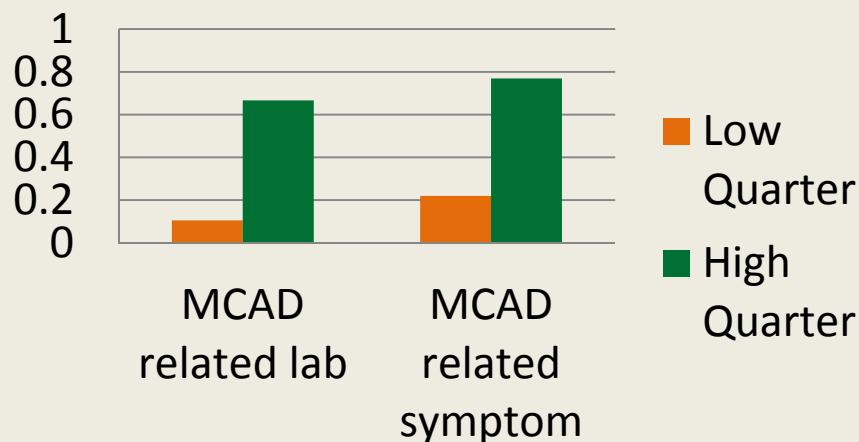
# IBEMC Accomplishments To Date

- 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](http://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

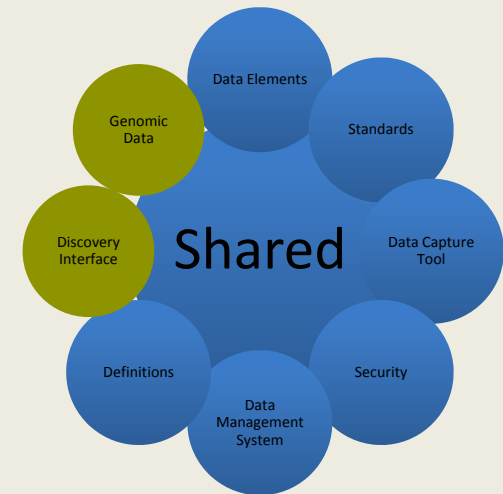
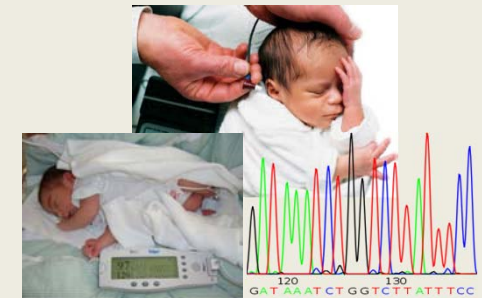
- **Revisit data sharing** with NBSTRN and revise data sharing plan if indicated
- Implement data sharing plan
- **Migration of legacy data** to NBSTRN LPDR according to IBEMC data sharing plan
- **Continue work of research study teams** and other research as opportunities present
- **Continue collaboration 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

The screenshot shows the NBSTRN website with a purple header. The main navigation bar includes links for Home, About, Resources, Research Tools, Services, Education, and Research Projects. A search bar is located on the right. The left sidebar lists various resource categories: Resources, State Profiles, Newborn Screening Publications, Disease Registries, Gaps in Research, Links, and SCID Resources. The main content area is titled "SCID Resources" and features a "Statement of Work for National SCID Pilot Study" with a list of links to educational resources for Severe Combined Immunodeficiency (SCID) associated with T Cell Lymphopenia.

This screenshot displays the "Virtual Repository of Dried Blood Spots" page. It features a dark header with the NBSTRN logo and navigation options: Home, About, Research Support, and Search. The main content area has a dark background and includes the text "REQUEST DRIED BLOOD SPOTS FOR RESEARCH" and "Search and request de-identified residual dried blood spots (DBS) to use in newborn screening related research projects." A "Register Now" button is visible at the bottom.

The screenshot shows the "Longitudinal Pediatric Data Resource" page. It features a purple header with the NBSTRN logo and the text "NBSTRN NEWBORN SCREENING TRANSLATIONAL RESEARCH NETWORK". The main content area displays a grid with a line graph showing growth curves for children. Below the graph, there are images of a baby in a crib, a baby crawling, a baby sitting up, and a young girl standing.

[www.nbstrn.org](http://www.nbstrn.org)

# Acknowledgments

- The NBSTRN-CC 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).
- The Inborn Errors of Metabolism Collaborative: Defining the Natural History of IBEM is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health Grant Number 5R01HD069039-02.
- The NCC is funded by U22MC24100, awarded as a cooperative agreement between the Maternal and Child Health Bureau/Health Resources and Services Administration, Genetic Services Branch, and the American College of Medical Genetics.
- Region 4 (Midwest) Newborn Screening and Genetics Collaborative is funded by the Health Resources and Services Administration (HRSA) Maternal and Child Health Bureau (MCHB) grant U22MC03963/H46MC24092.
- HRSA/MCHB Cooperative Agreements to the following Regional Newborn Screening and Genetics Collaboratives: New York-Mid-Atlantic, Heartland, and Region 4 (Midwest).
- Both the R4NBSGC and IBEMC are projects of the Michigan Public Health Institute.

# Acknowledgements (continued)

## IBEMC Members and Contributors

- Susan A. Berry

## Michigan Public Health Institute

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



## Joint Committee

- NCC/RC LTFU Data Workgroup
- NBSTRN Clinical Centers Workgroup

## NBSTRN

- Michael Watson
- Amy Brower
- Amy Hoffman
- Bruce Bowdish

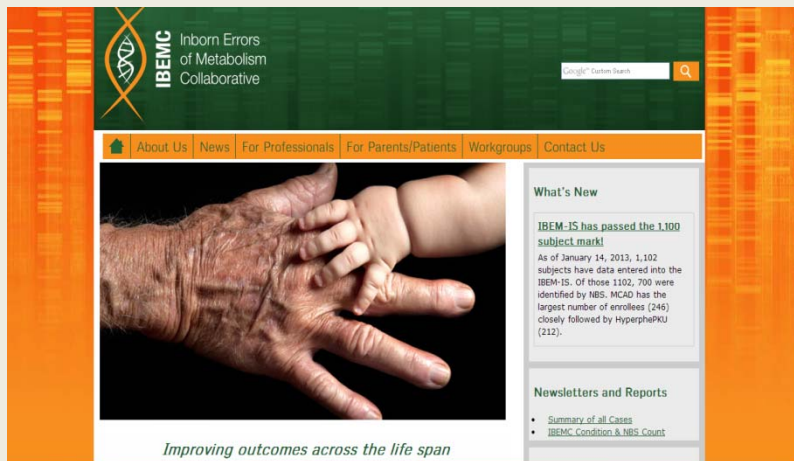
## CHOP

- Jen Loutrel
- Stacey Wrazien
- Peter White
- Jeff Pennington
- Mark Porter

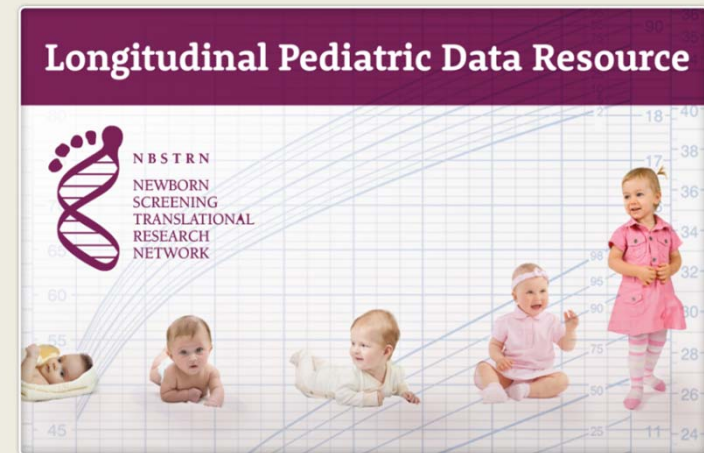
# Thank You!

[www.ibem-is.org](http://www.ibem-is.org)

[www.nbstrn.org](http://www.nbstrn.org)



The screenshot shows the homepage of the Inborn Errors of Metabolism Collaborative (IBEM-IS). The header features the IBEM-IS logo and the text "Inborn Errors of Metabolism Collaborative". A navigation menu includes "About Us", "News", "For Professionals", "For Parents/Patients", "Workgroups", and "Contact Us". The main content area has a large image of an elderly hand holding a baby's hand, with the tagline "Improving outcomes across the life span". A "What's New" section reports that IBEM-IS has passed the 1,100 subject mark, with 1,102 subjects entered as of January 14, 2013. A "Newsletters and Reports" section lists "Summary of all Cases" and "IBEM-IS Condition & NBS Count".



The banner for the NBSTRN Longitudinal Pediatric Data Resource features a purple header with the title "Longitudinal Pediatric Data Resource". Below the header is the NBSTRN logo, which consists of a purple footprint and a DNA double helix. The text "NBSTRN NEWBORN SCREENING TRANSLATIONAL RESEARCH NETWORK" is displayed. The background is a grid with a blue line graph showing growth curves. At the bottom, there are images of a baby in a crib, a crawling baby, a sitting baby, and a standing toddler.

