IBEMC Inborn Errors of Metabolism Collaborative

NBSTRN NEWBORN SCREENING TRANSLATIONAL RESEARCH NETWORK

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

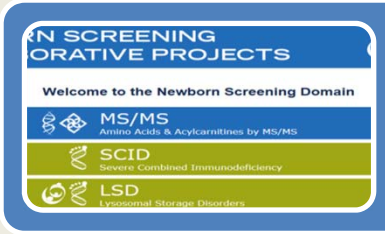
IBEMC

- 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

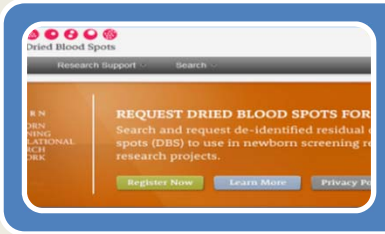
NBSTRN

- 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)

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

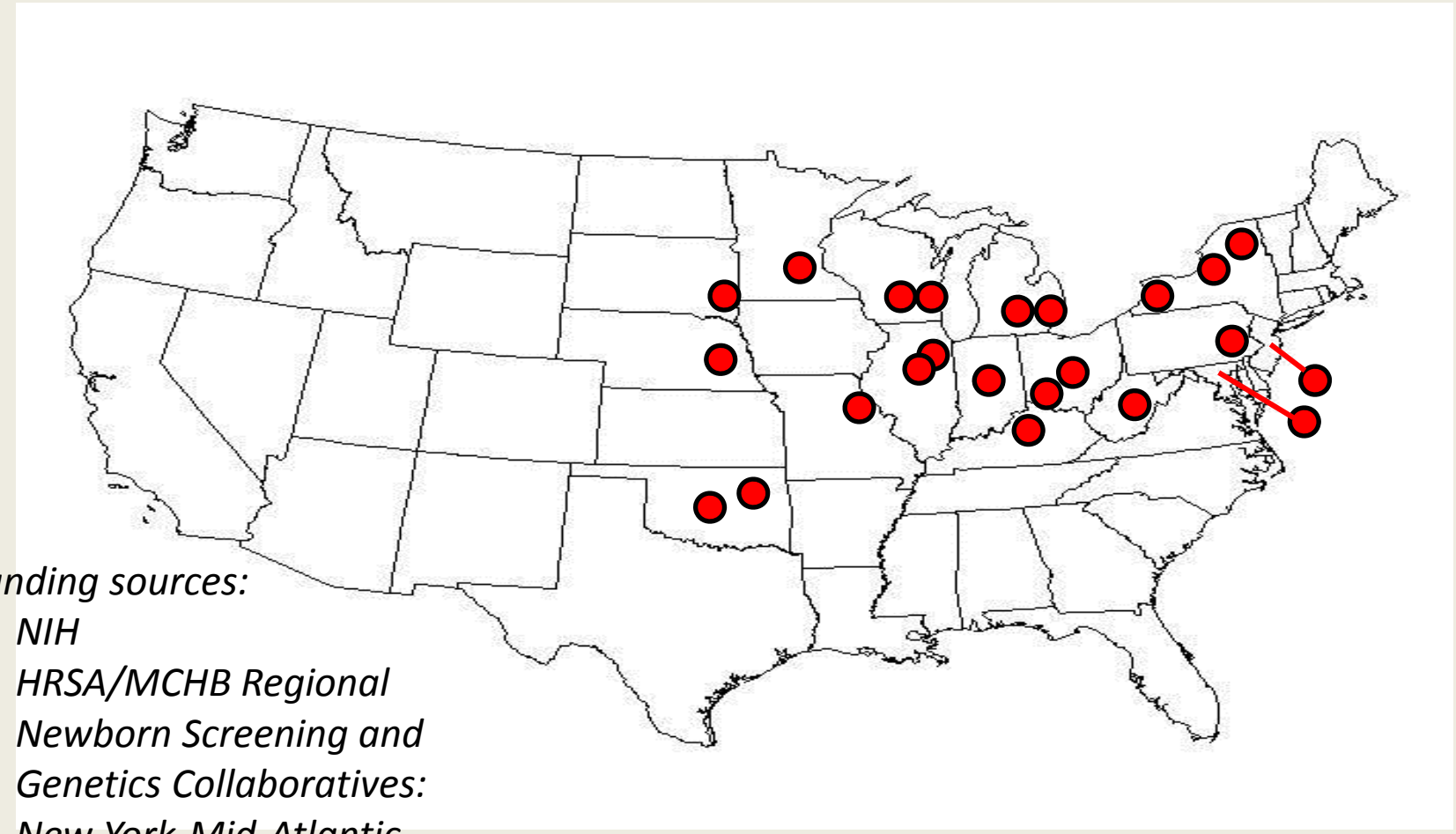
Added new centers supported by other Regional Genetics Collaboratives (HRSA, NYMAC)

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

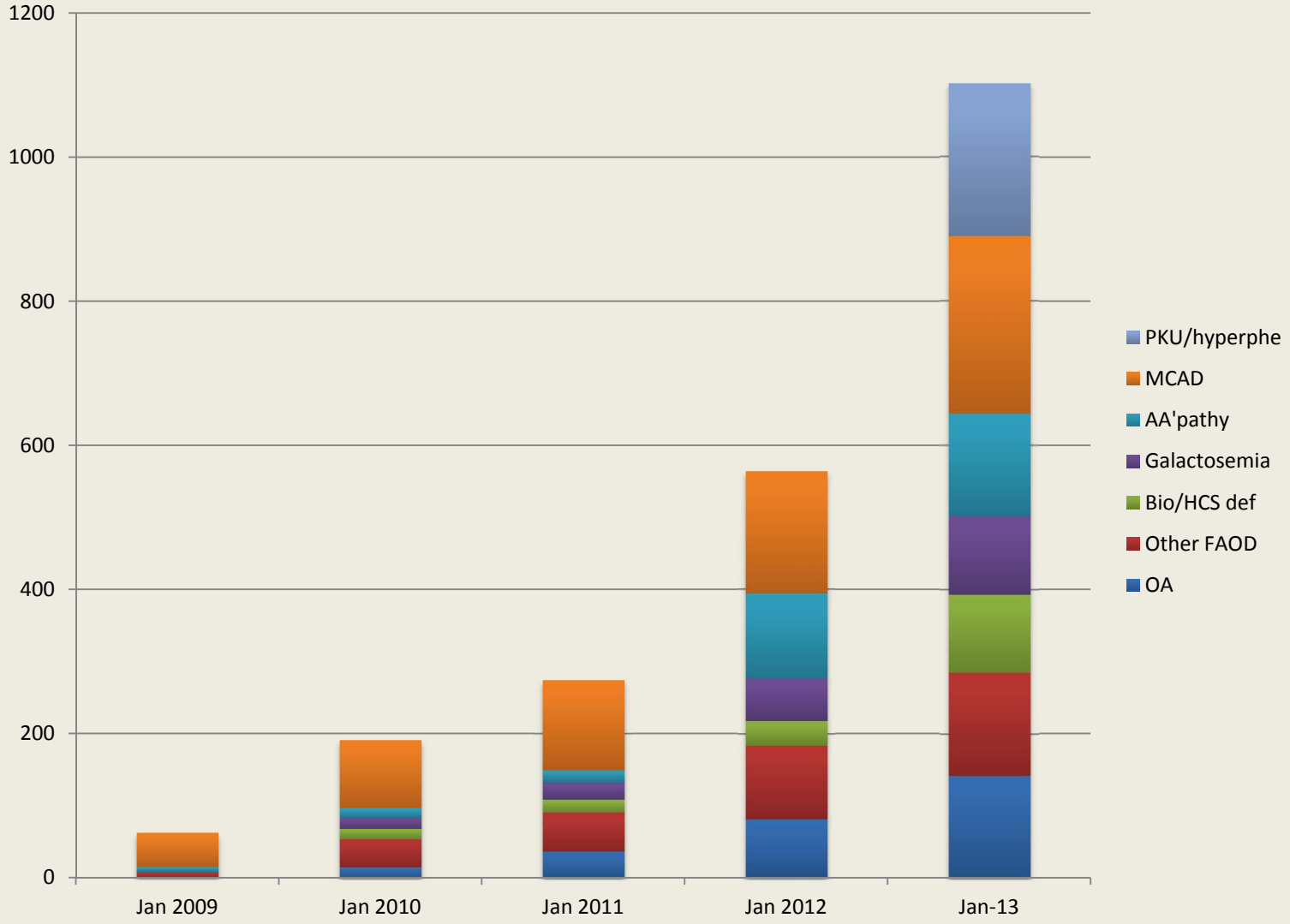


Funding sources:

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

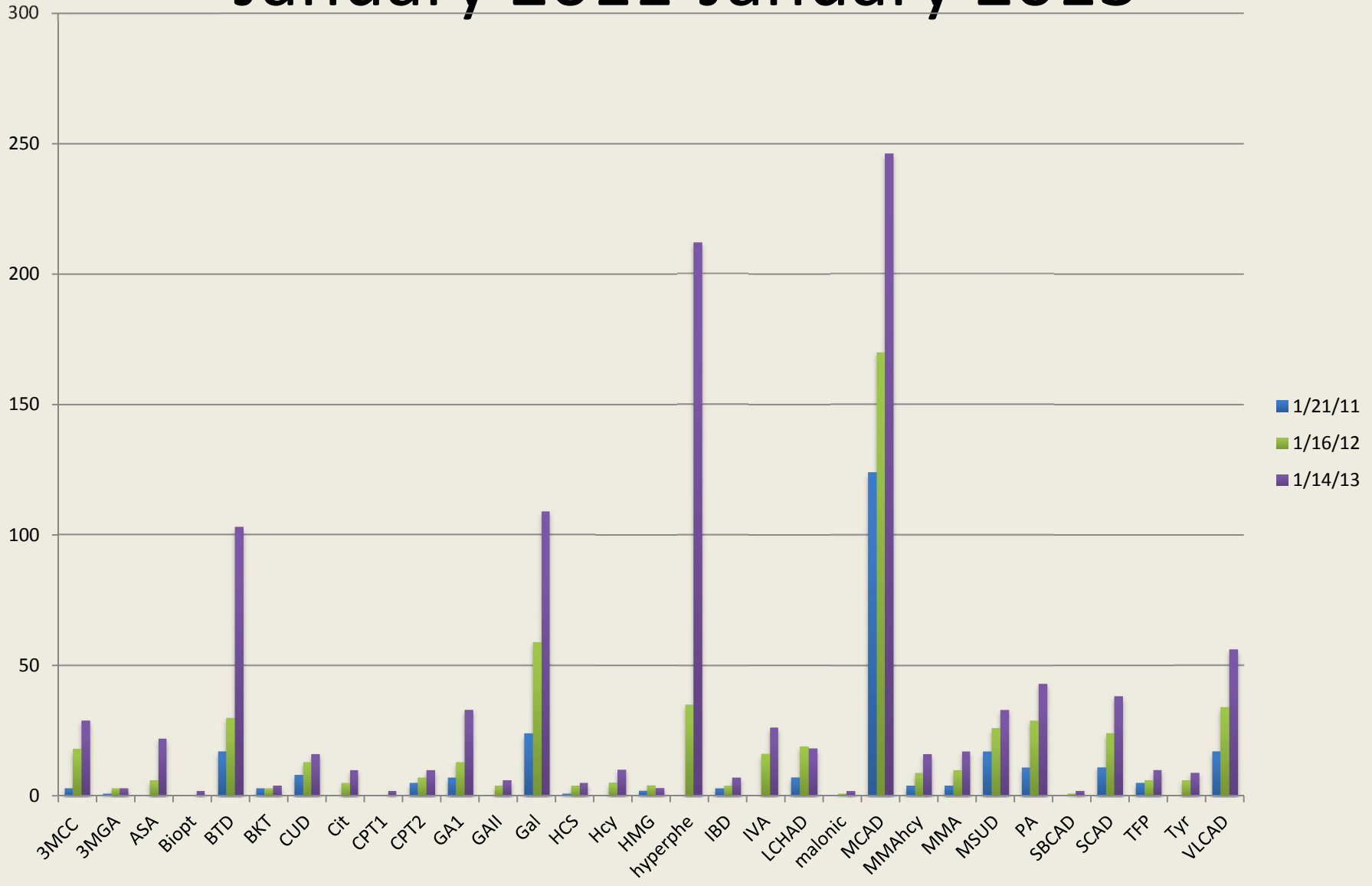
IBEMC Inborn Errors of Metabolism Collaborative

IBEMC Case Enrollments January 2009-January 2013



IBEMC Inborn Errors of Metabolism Collaborative

IBEMC Cases by Condition January 2011-January 2013



IBEMC Condition Count & NBS Ascertainment

3MCC	29		GAII	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		HyperphePKU	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

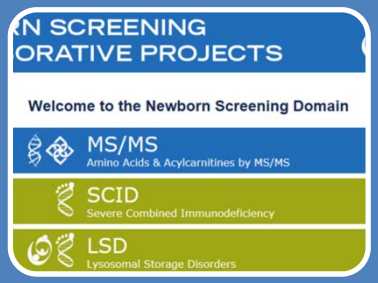
- Current efforts
  - Natural history of newborn screened disorders
  - Novel technologies
  - Newborn screening pilots

- 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



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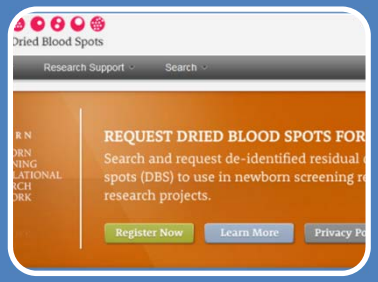

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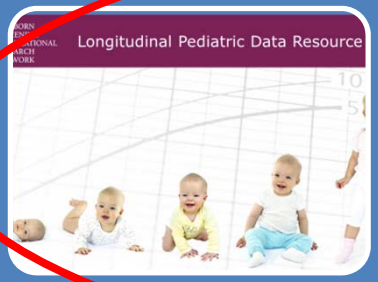


LPDR

- Secure, standards-based clinical data collection and management
- Aggregate, share, and analyze data

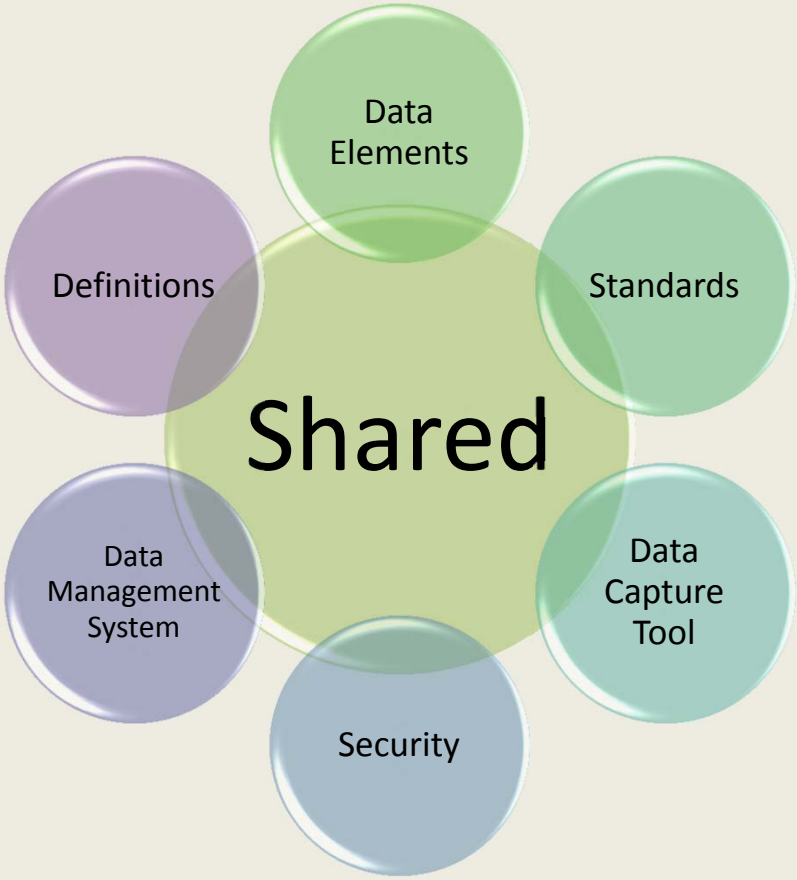
Key IBEMC-LPDR Components

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

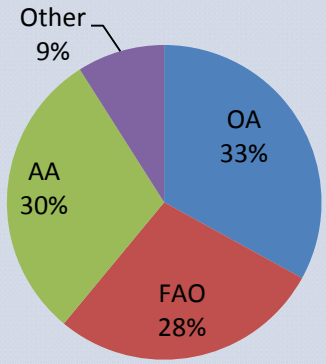
Implementation, continuous R & R

Consent templates, MOU, SOP

Longitudinal Pediatric Data Resource (LPDR)

Common Data Elements (CDEs)

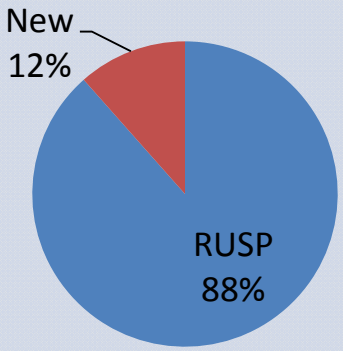
- Available
  - 46 RUSP



  - 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:

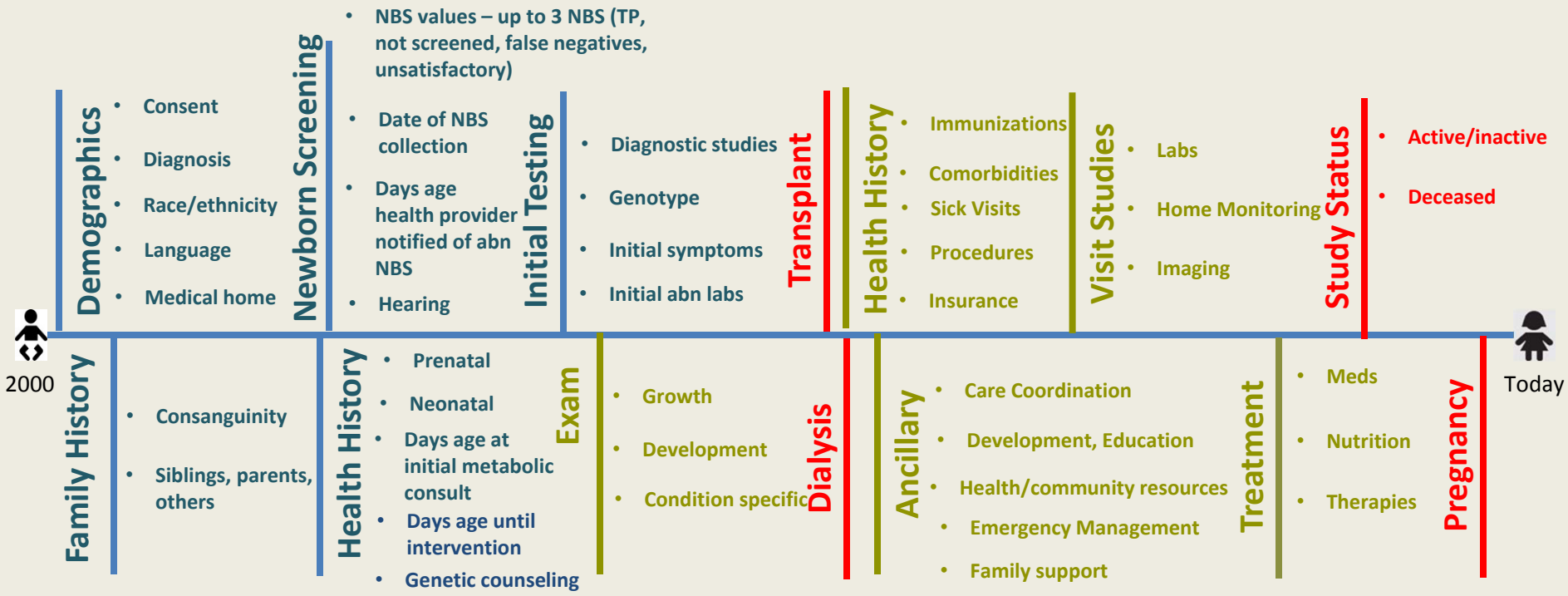
- Families
- Laboratory specialists
- Public health
- Clinicians
- Follow-up coordinators
- Informatics
- Educators
- **NBS advocates**
- Researchers
- Quality improvement/assurance specialists
- Many others

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

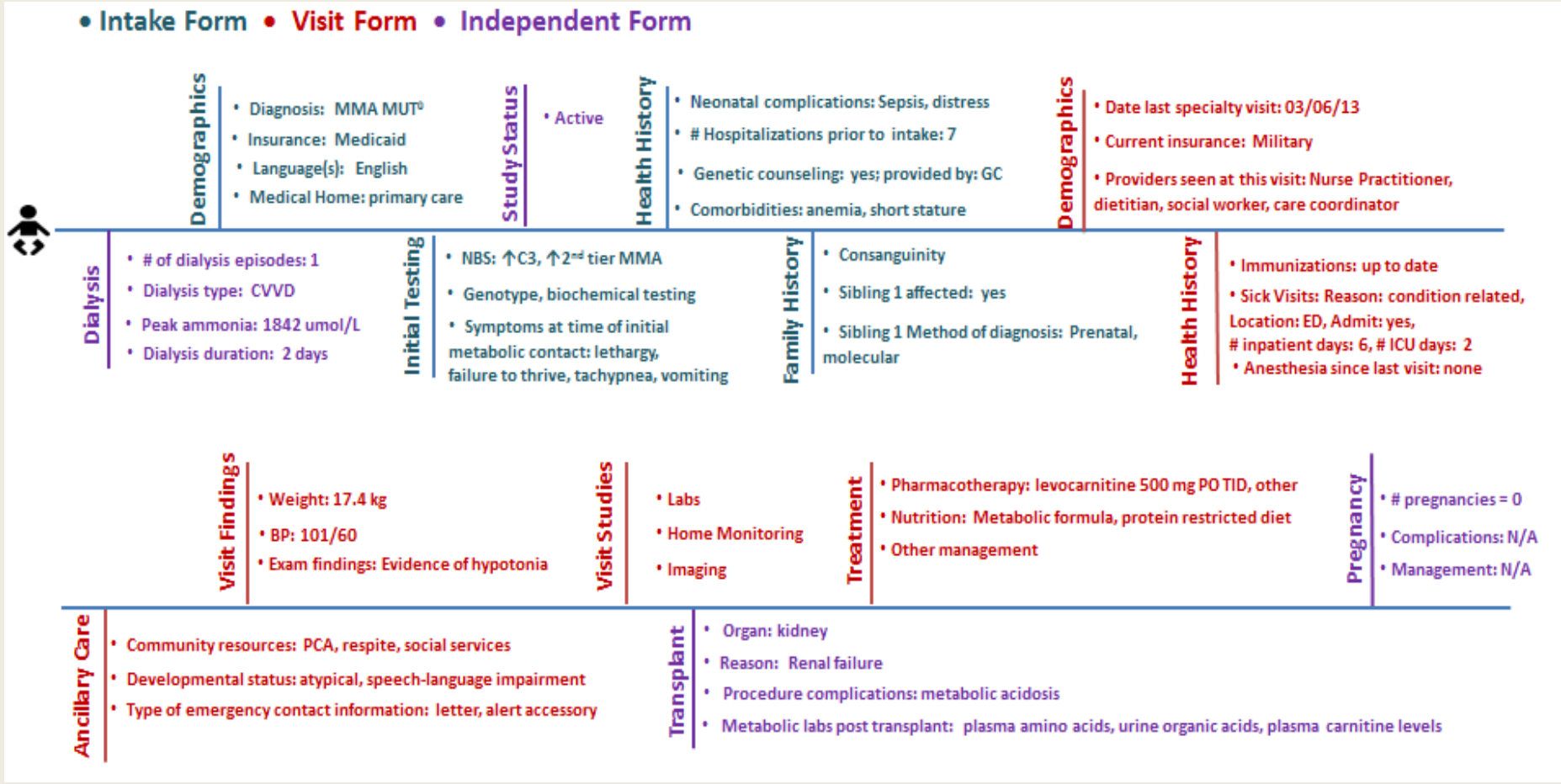
LPDR Case Report Forms

Subject | Longitudinal Care Record

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



IBEMC Mock Case Example: Methylmalonic Acidemia (MUT)



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)

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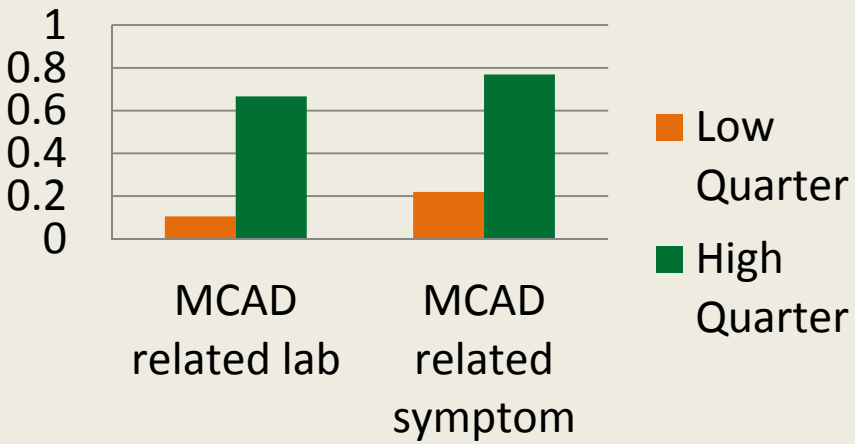
Example of IBEMC Project Findings: MCAD Deficiency (data collected from 2007-2013)

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

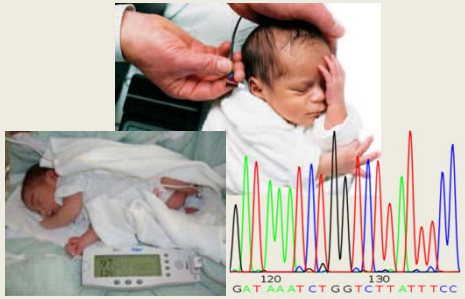
- **Revisit data sharing** with NBSTRN and revise data sharing plan if indicated
- Implement data sharing plan
- **Migration of legacy data** to NBSTRN LPDR according to IBEMC data sharing plan
- **Continue work of research study teams** and other research as opportunities present
- **Continue collaboration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

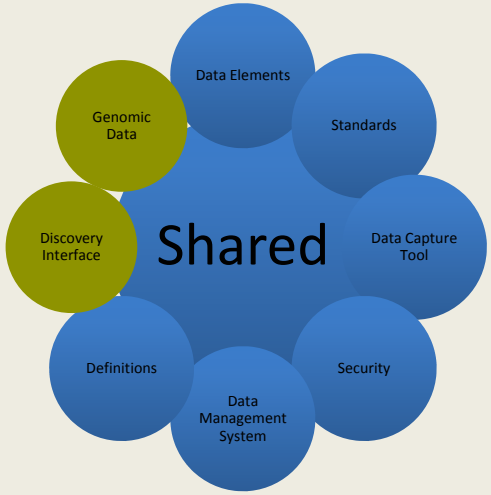
NBSTRN Accomplishments to Date

- 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**

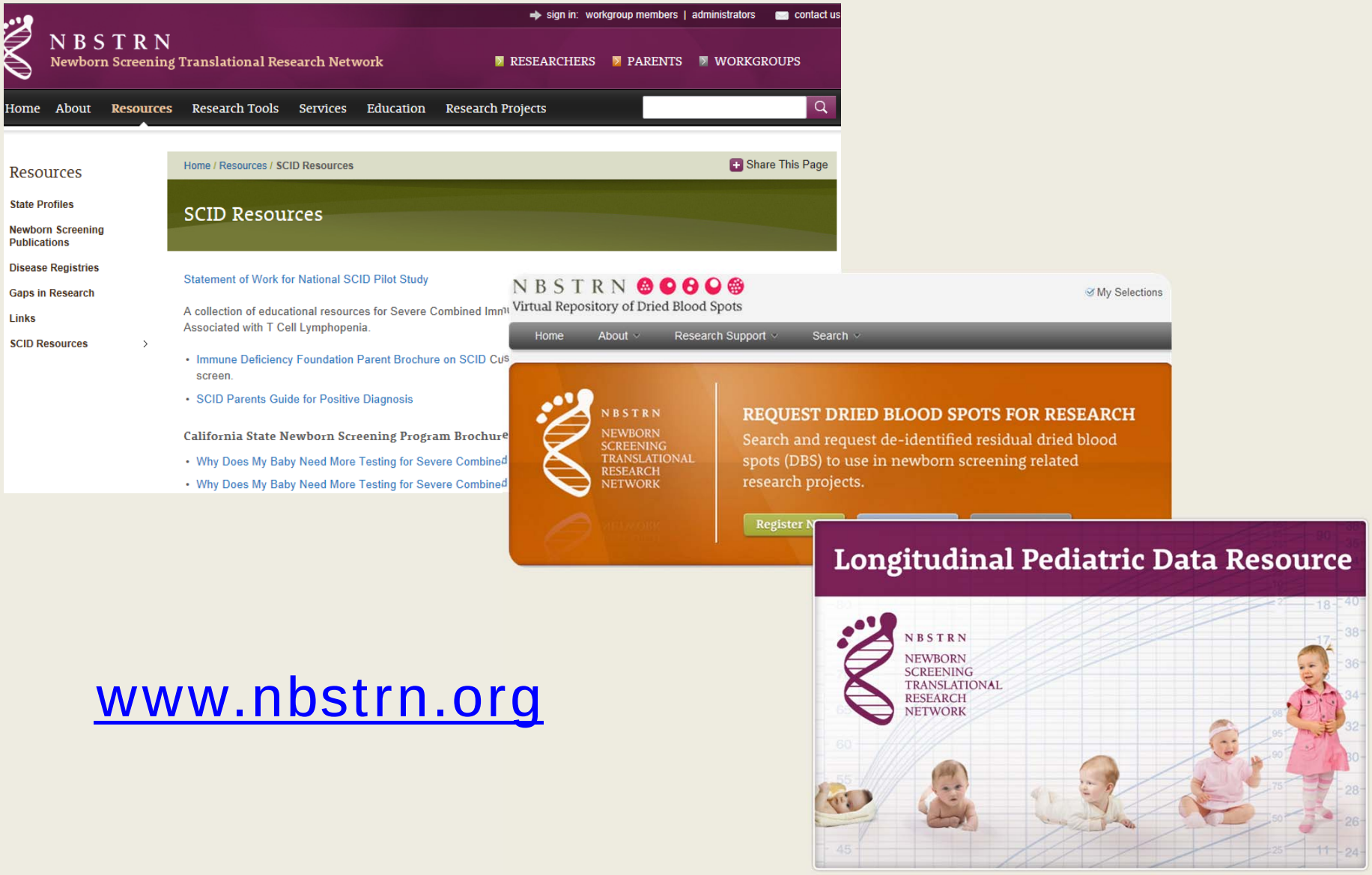
IBEMC Partnership

- **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



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Acknowledgments

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- **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.**

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- **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

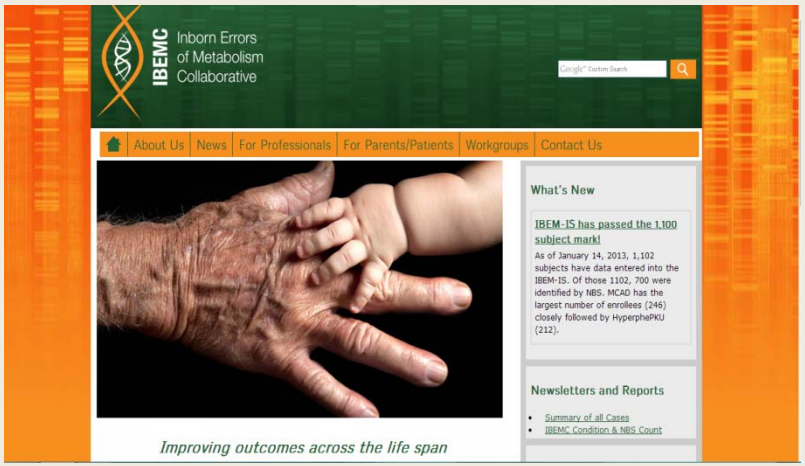
Family Participants

CHOP

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

Thank You!

www.ibem-is.org



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