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

Susan A. Berry for the IBEMC

Michigan Public Health Institute
Okemos, MI

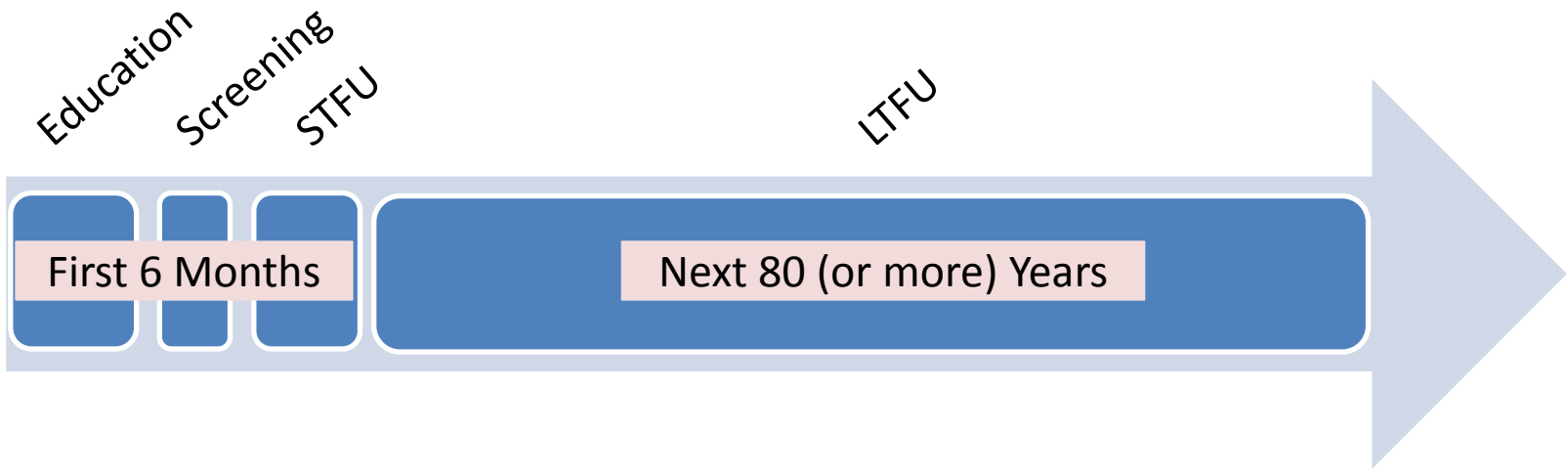
IBEMC Inborn Errors of Metabolism Collaborative

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



(not drawn to scale!!)

NCC
National Coordinating Center
for the Regional Genetic Service Collaboratives

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

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

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*

IBEMC Inborn Errors of Metabolism Collaborative

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

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

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

ACMG

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

IBEMC Inborn Errors of Metabolism Collaborative

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

NBSTRN
Newborn Screening Translational Research Network

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

IBEMC Inborn Errors of Metabolism Collaborative

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

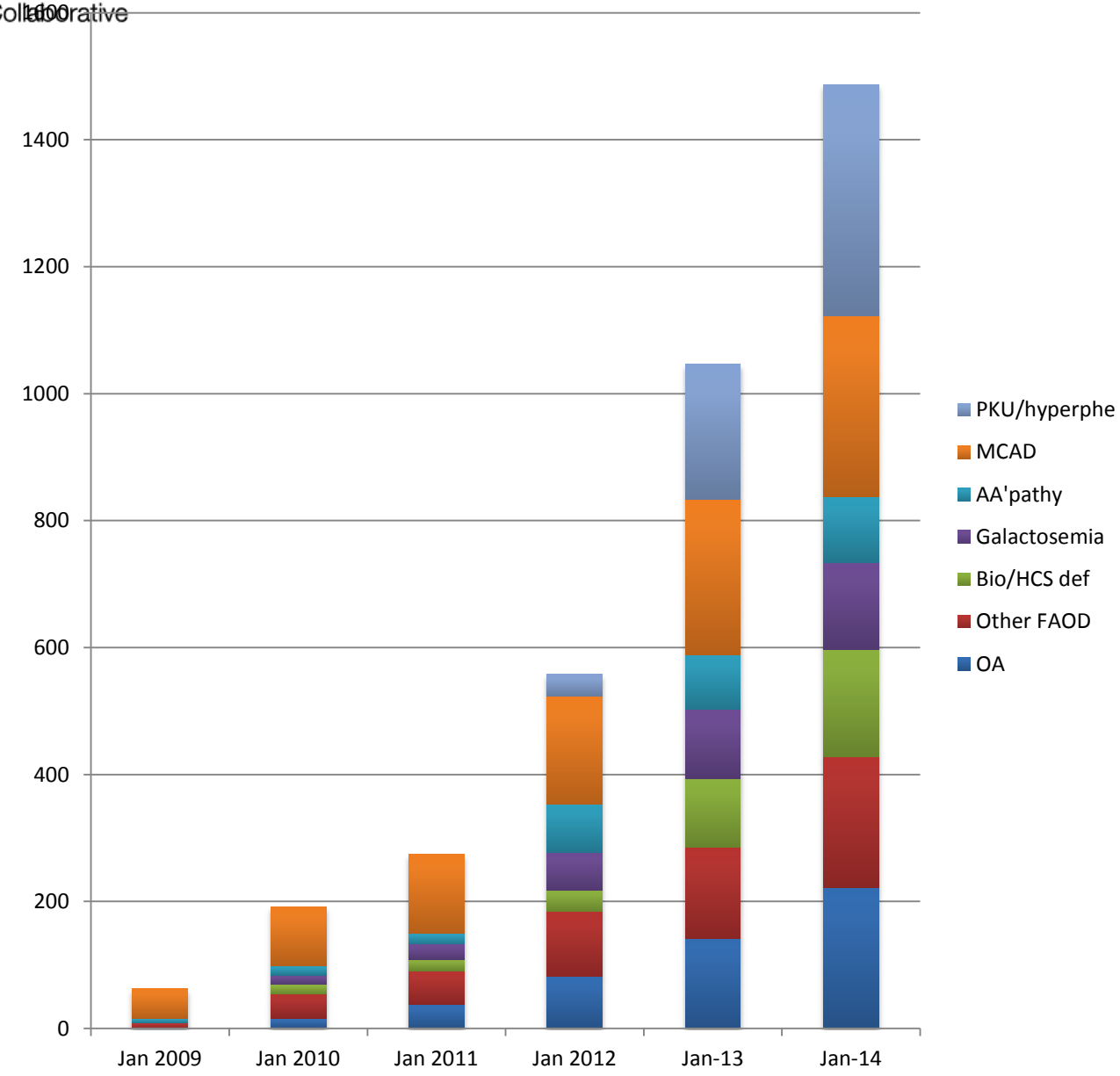
Methylmalonic acidemia (Cbl C,D)
2M3HBA deficiency
IBG deficiency
2MBCAD deficiency
3-Methylglutaconic aciduria
Malonic acidemia

Other

GalE, GalK

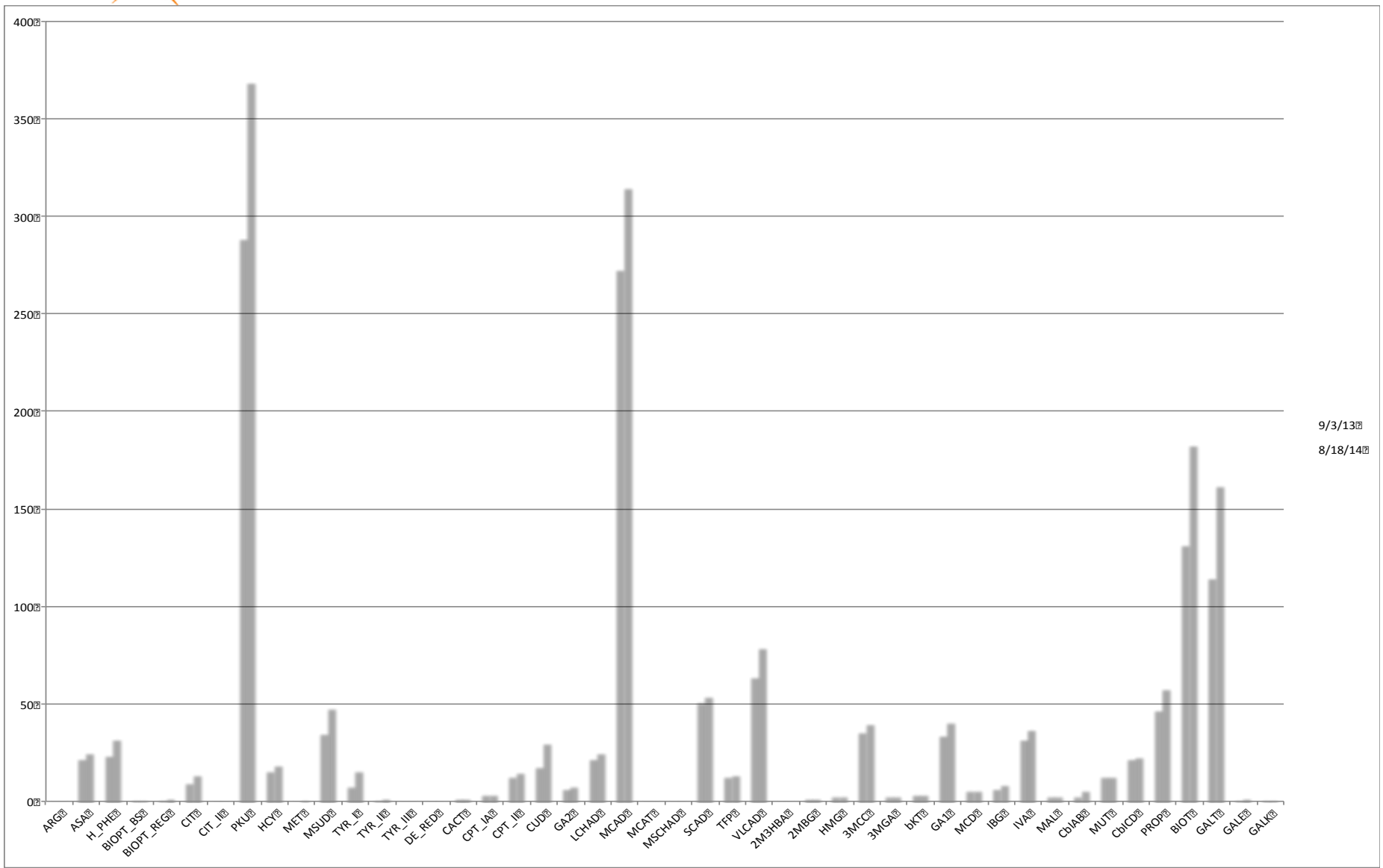
IBEMC Inborn Errors of Metabolism Collaborative

Jan 2009-Jan 2014



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

IBEMC Inborn Errors of Metabolism Collaborative

Data: Numbers and Contacts

Query	# With finding	Total with data	% of Total
Agree to re-contact		941	
Yes	759		81%
No	182		19%
Diagnosis by		1341	
NBS	1096		82%
Family member	74		6%
Clinical	152		11%
Lab	19		1%
Genetic counseling		1304	
Yes	1175		90%
No	50		4%
Unk	79		6%

Time to Intervention

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

IBEMC Inborn Errors of Metabolism Collaborative

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

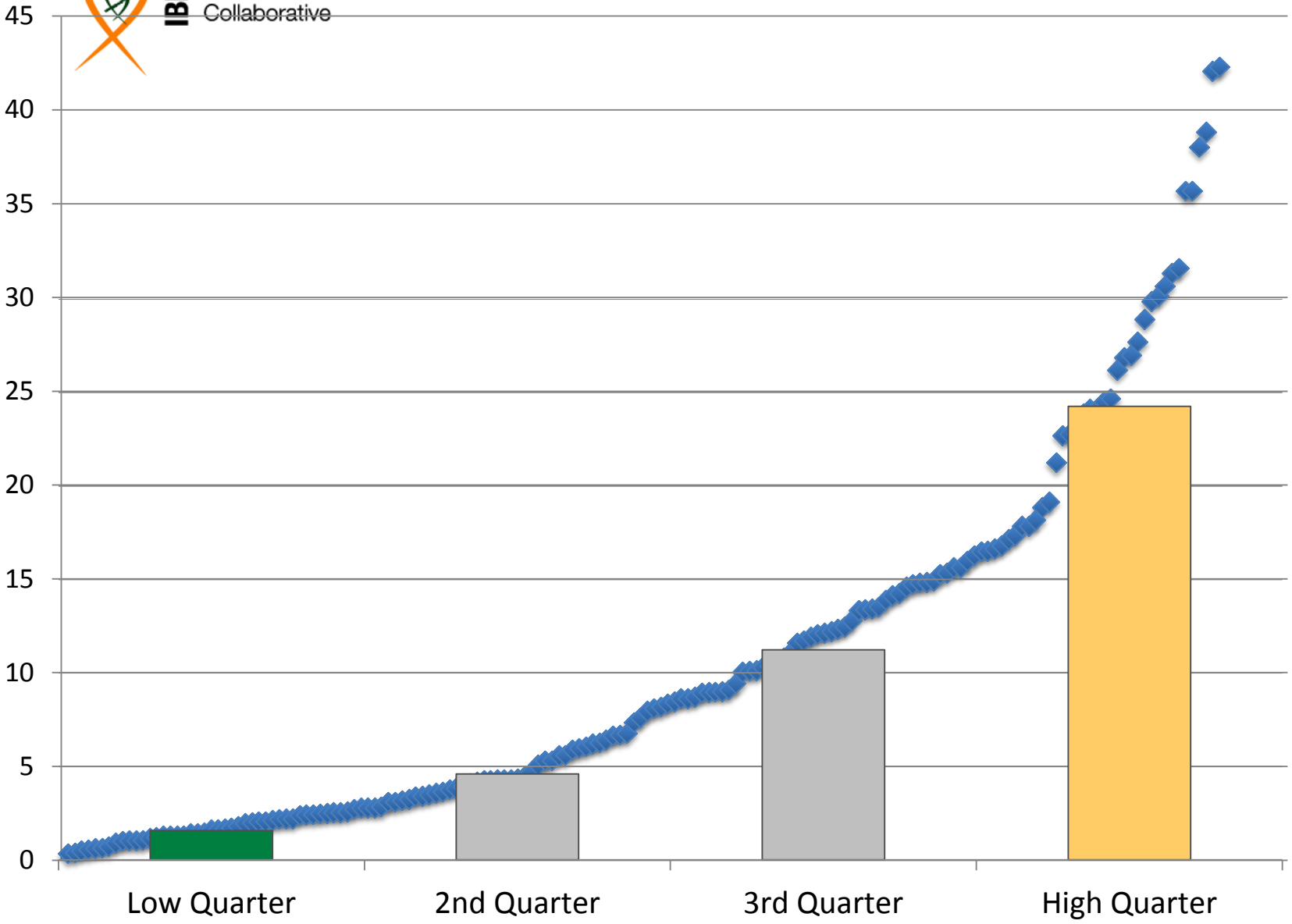
- If deceased, date of death
- Mutation description: Allele 1, Allele 2
- C8 on first NBS
- Lab abnormalities at time patient or primary care provider (on behalf of patient) first contacts metabolic specialist *(multicheck box+"other")*
- Symptom(s) at time of initial metabolic contact *(multicheck box+"other")*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

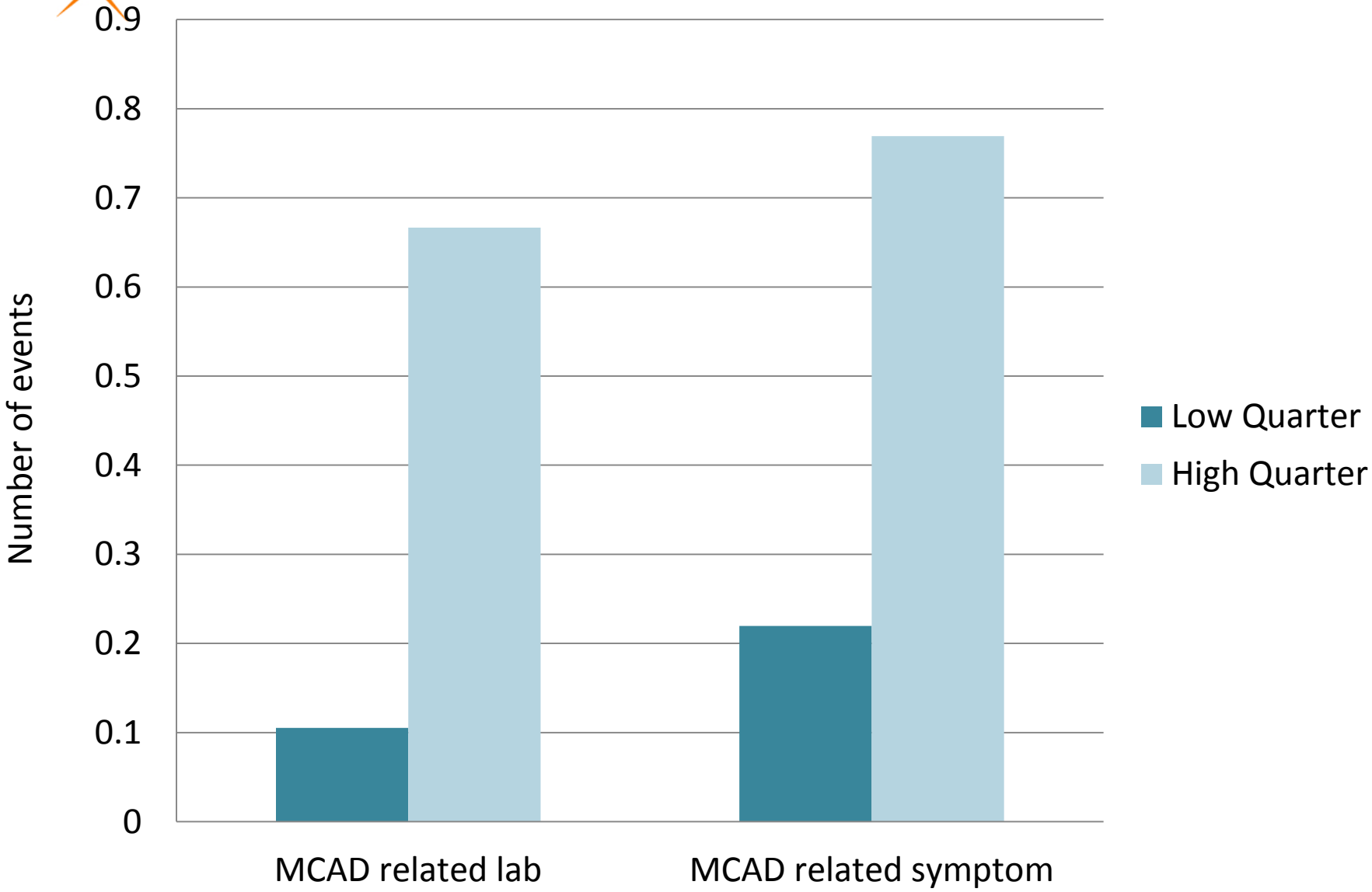
IBEMC Inborn Errors of Metabolism Collaborative

C8 values on NBS (µmol/L)



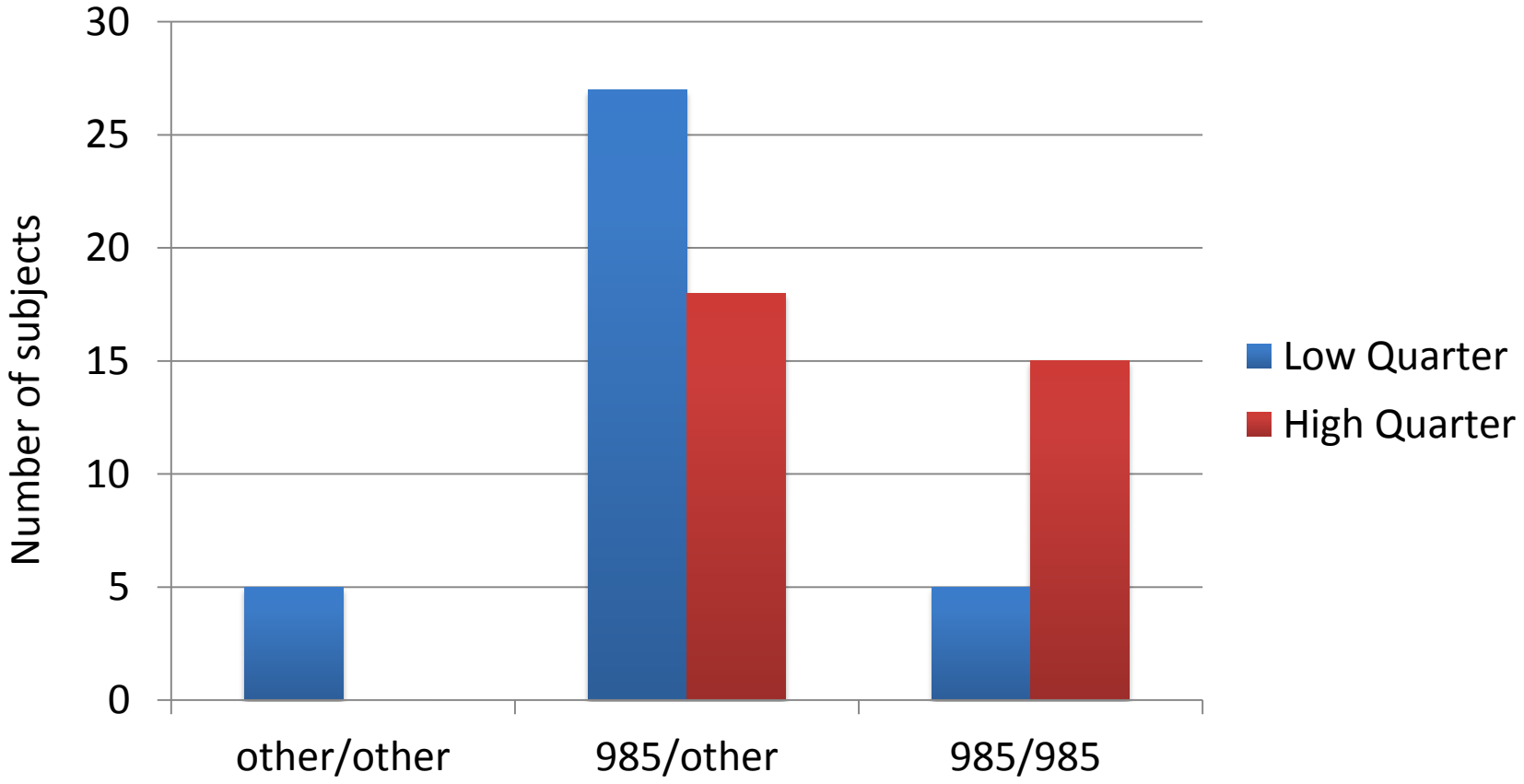
IBEMC Inborn Errors of Metabolism Collaborative

MCADD-related Symptoms or Labs



IBEMC Inborn Errors of Metabolism Collaborative

Number of 985A>G alleles



IBEMC 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?

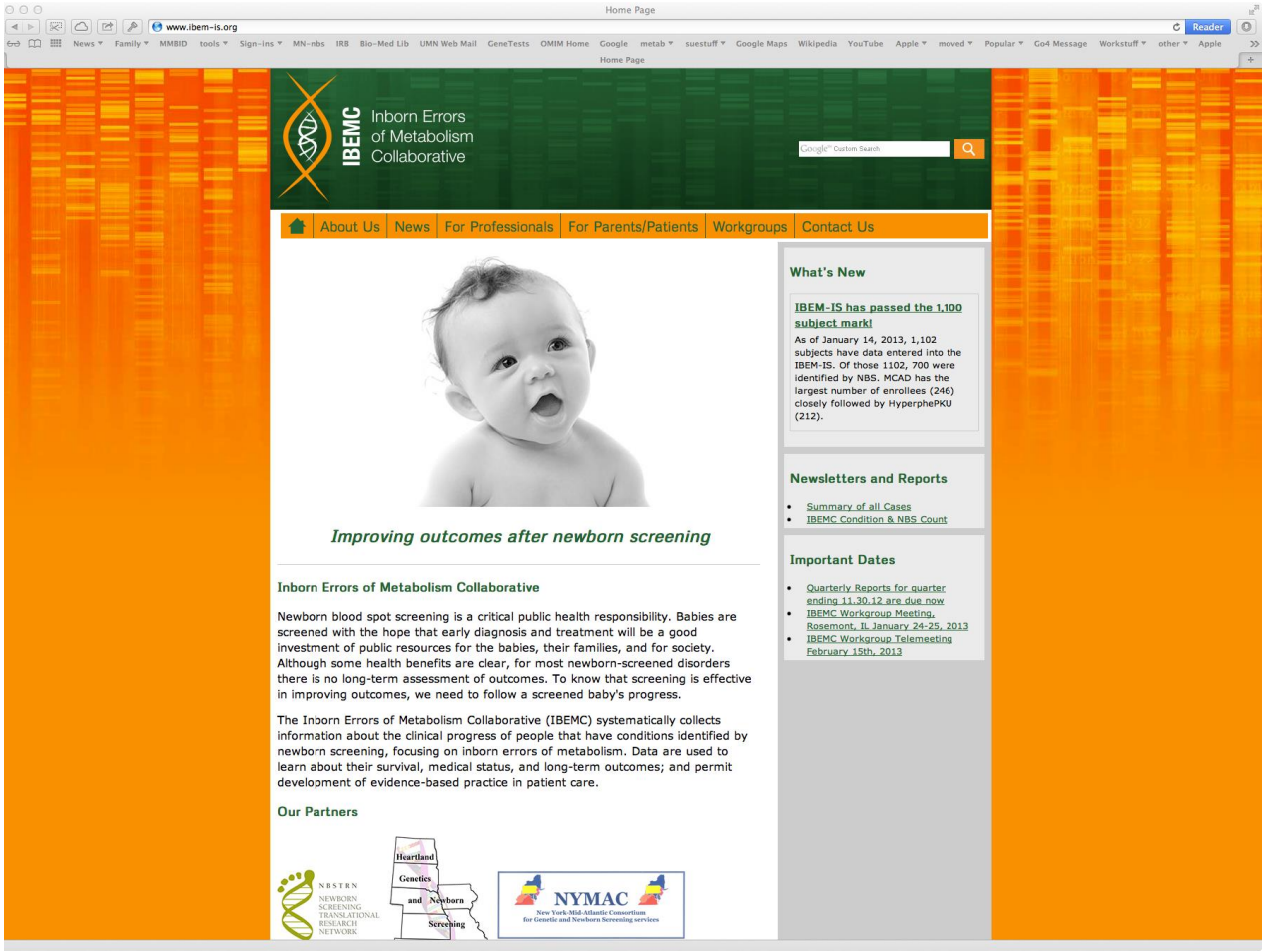
- New accomplishment via IBEMC collaboration with NBSTRN
  - Using REDCap web-based data collection (“instance” at MPHI)
- Added condition-specific research programs

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:

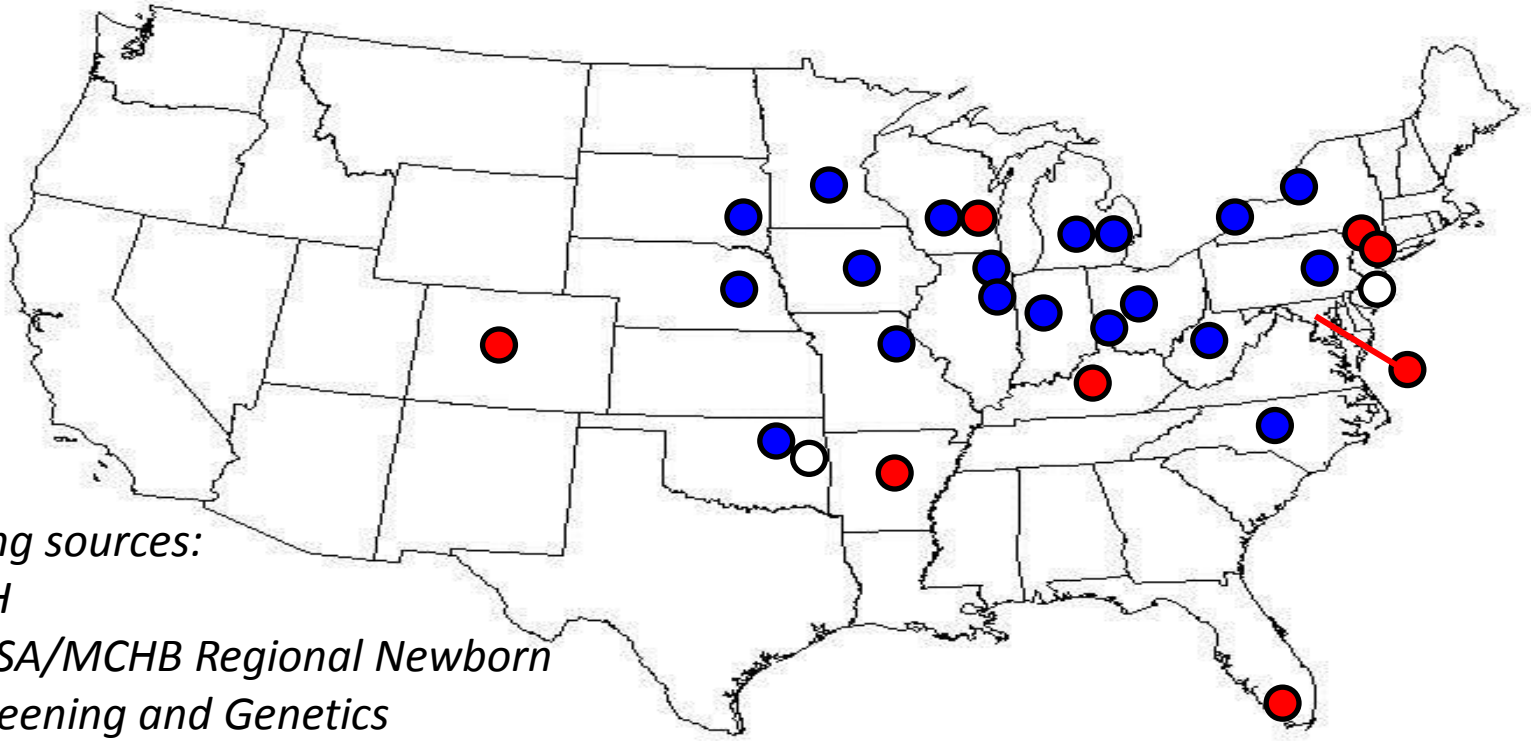
www.ibem-is.org



IBEMC Inborn Errors of Metabolism Collaborative

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

IBEMC Inborn Errors of Metabolism Collaborative

Clinic	Clinician	Res. Coordinator
Arkansas Children's Hospital	Stephen Kahler	Suzanne Huetter
Children's Hospital Colorado	Janet Thomas	Erica Wright
University of Iowa Health Care	Alvero Serano-Russi	Emily Phillips
*Lurie Children's Hospital of Chicago	Barbara Burton	Clare Edano; Sheela Shrestha
*University of Illinois	George Hoganson	Lauren Kime
*Indiana University	Bryan Hainline	Susan Romie
University of Louisville	Alexander Asamoah	Kara Goodin; Cecelia Rajakaruna
Johns Hopkins	Ada Hamosh; Hilary Vernon	TBN
*University of Michigan	Ayesha Ahmad	Sue Lipinski
*Wayne State University, Michigan	Gerald Feldman	TBN
*University of Minnesota	Susan Berry	Sara Elsbecker
*University of Missouri	Richard Hillman	Dawn Peck
*Duke University	Loren Pena	Mimi Coker
University of Nebraska	Machelle Zink	Nancy Kay Ambrose
Children's Hosp. at Montefiore (NY)	Paul Levy	TBN
New York Medical College	David Kronn	
University of Rochester	Chin-to Fong; Kristin D'Aco	Eileen Blakely
Women & Children's Hospital of Buffalo	Richard Erbe	TBN
*Cincinnati Children's Hospital	Nancy Leslie	Racheal Powers
*Nationwide Children's Hospital	Dennis Bartholomew	Jimia Hoy
University of Oklahoma	Klaas Wierenga	Aimee Babarsky
*University of Pittsburgh	Georgianne Arnold	Cate Walsh-Vockley
*Sanford Children's Specialty Clinic	Laura Keppen	Quinn Stein
Medical College of Wisconsin	Bill Rhead	Abby Donovan
*University of Wisconsin	Sandy VanCalcar	Sara Jadin
West Virginia University	TC Narumanchi; Marybeth Hummel	Jennie Wilkens

Acknowledgements (2)

- Cynthia Cameron – CoPI
- Sally Hiner – Project Coordinator
- Kristi Bentler – Clinical Consultant
- Shaohui Zhai – Project Statistician
- MPHI Staff

The IBEMC is a project of the Michigan Public Health Institute

Funded by NIH 1R01HD069039 and

HRSA/MCHB Cooperative Agreements to the following Regional Newborn Screening and Genetics Collaboratives:

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

The NBSTRN is funded by NIH-HHSN27520130001C