CONSENSUS CASE DEFINITIONS FOR CONDITIONS IDENTIFIED BY NEWBORN SCREENING PUBLIC HEALTH SURVEILLANCE

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BACKGROUND

- Case definitions for Public Health Surveillance Newborn Screening were developed through expert workgroups, under leadership from HRSA
- Presented to ACHDNC in May and September 2012

IMPLEMENTATION

- NewSTEPs has incorporated the Case Definitions into a National Repository
- NewSTEPs is also assisting states to develop systems for implementation of case definitions at state level

SURVEILLANCE VS. CLINICAL CASE DEFINITION

- Surveillance case definitions are intended to establish uniform criteria for *disease reporting*

- NOT intended for use as
  - criteria for establishing clinical diagnoses
  - determining the standard of care necessary for a particular patient
  - setting guidelines for quality assurance
  - providing standards for reimbursement
  - initiating public health actions

EXAMPLE: CYSTIC FIBROSIS

EXAMPLE IN CYSTIC FIBROSIS

- Newborn with abnormal newborn screen:
  - Immunoreactive trypsinogen (IRT) 105 ng/mL (normal range < 60 ng/mL)
  - NBS DNA analysis revealed F508/R117H, 7T/9T
- Abnormal NBS called out to pediatrician
  - Referred to CF Center for Sweat Test
  - Sweat test results: 32mmol/L (diagnostic > 60mmol/L)

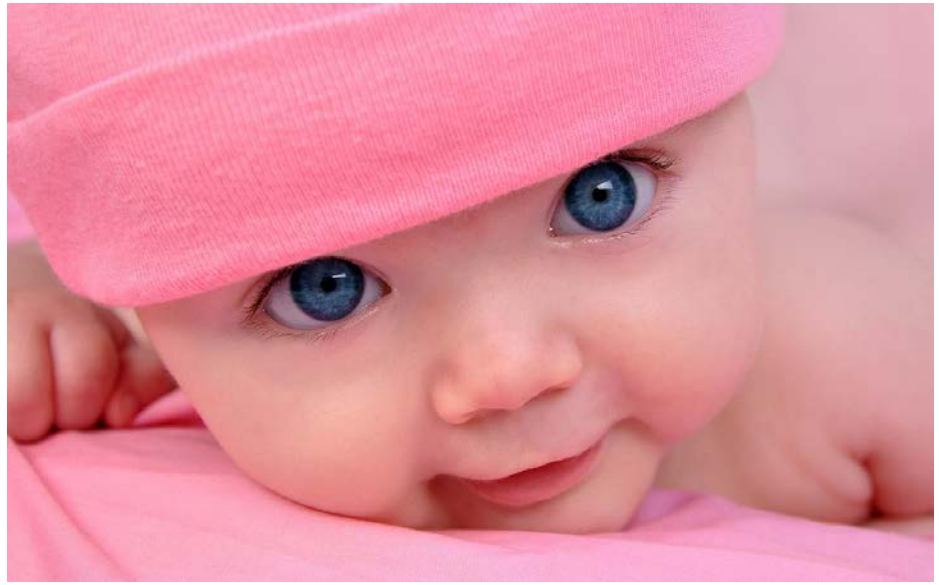
DIAGNOSTIC DIFFERENCES

- Baby seen by Dr. Smith: Baby likely has CF. Follow monthly and repeat sweat test; tell family baby has CF.
- Baby seen by Dr. Jones: Baby has CRMS (Cystic Fibrosis Related Metabolic Syndrome). Not CF, we should follow this baby every 6 months to see if baby develops CF symptoms
- Baby seen by Dr. Garcia: Baby is fine, no CF, no CRMS. No diagnosis, baby does not need to be seen.

HOW SHOULD PUBLIC HEALTH PROGRAMS COUNT THAT INFANT?

- Clinicians treat the patient as they believe is best for the baby and the family

- Public Health Surveillance needs to count babies systematically, not based on clinical opinion



APPLICATION OF THE CASE DEFINITIONS TO THIS CASE

- Infant would be considered to have CRMS
- Not CF based on information provided
- Programs are encourage to assess diagnosis at 1 year of age

WHY HAVE SURVEILLANCE CASE DEFINITIONS?

- In order to:
  - accurately monitor the trends of reported diseases,
  - detect their unusual occurrences
  - define a uniform population in order to allow for the evaluation of intervention.
- Usefulness depends on uniformity, simplicity and timeliness
- Necessary as we combine data from multiple sources, for a state/region comparisons, or comparisons over time

DEVELOPMENT OF THE CASE DEFINITIONS

INITIATION OF THE PROCESS

- June 2011 HRSA convened gatherings of subject matter experts from the Regional Genetics Collaboratives
  - Hematologists
  - Metabolic Geneticists
  - Pulmonologists
  - Immunologists
  - Endocrinologists
- Discuss potential case definition models
  - Quantitative, tier, diagnostic

RESOURCES THAT INFORMED THE PROCESS

- Mountain States Regional Genetics Collaborative Disease-Specific Care Plans
- Region 4 Stork Data System
- California Metabolic Group case definitions
- New York and Mid-Atlantic Collaborative clinical guidelines
- American College of Medical Genetics and Genomics ACTion Sheets consensus-based guidelines
- CDC 4-States Pilot project

SEVERAL MODELS CONSIDERED

- Tiered model: tier definitions based on certainty of definitions, based on the extent of the diagnostic workup and accompanying results.
- Quantitative model: points would be assigned based on diagnostic test criteria and the interpretation of those results based upon a predetermined scale.
- Diagnostic models: based on previously published regional or state NBS projects

MEETINGS AND FEEDBACK

- Face-to-face (June 2011 All, Feb 2012 Metabolic)
- E-mails and conference calls (2012 – 2014)
- Case definitions sent to HRSA Regional Collaboratives (RCs), spring 2012
  - Areas of duplication
  - Additional criteria identified
- Presented to ACHDNC – May 2012 (Dr. Cindy Hinton)
- July 2012
  - Meeting of representatives from 35 NBS state programs and clinical representatives
  - Assess feasibility of applying NBS case definitions
- Presented to ACHDNC – September 2012 (Mr. Jelili Ojodu)

PILOTING THE CASE DEFINITIONS

- NewSTEPs piloted the definitions with ten state NBS programs in 2013.
- Data were collected using REDCap (a secure web based application).
- Retrospective data from past 2 years (maximum of 10 cases/disorder)
- Definitions underwent revision based on user feedback

PRODUCT

- Case Definition Tables for most of the initial RUSP Conditions (26/29)
- Classification tables are posted at www.newsteps.org

Metabolic Disorders		
Organic Acid Disorders	GA1: Glutaric acidemia type I	MMA without homocystinuria
	IVA: Isovaleric acidemia	PROP: Propionic Acidemia
	3-MCC: 3-methylcrotonyl-CoA carboxylase deficiency	MCD: Holocarboxylase synthase deficiency
	MMA with homocystinuria	
Fatty Acid Disorders	CUD: Carnitine uptake defect	TFP: Trifunctional Protein Deficiency
	MCAD: Medium-chain acyl-CoA dehydrogenase deficiency	VLCAD: Very long-chain acyl-CoA dehydrogenase deficiency
	LCHAD: Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (included in definition of TFP)	
Amino Acid Disorders	ASA: Argininosuccinic aciduria	MSUD: Maple syrup urine disease
	CIT: Citrullinemia, type I	PKU: Classic phenylketonuria
	HCY: Homocystinuria (CBS Deficiency)	TYR-1: Tyrosinemia, type I

Endocrine Disorders	Other Disorders	
CH: Primary congenital hypothyroidism	BIO: Biotinidase deficiency	CF: Cystic fibrosis
CAH: Congenital adrenal hyperplasia	GALT: Classic galactosemia	

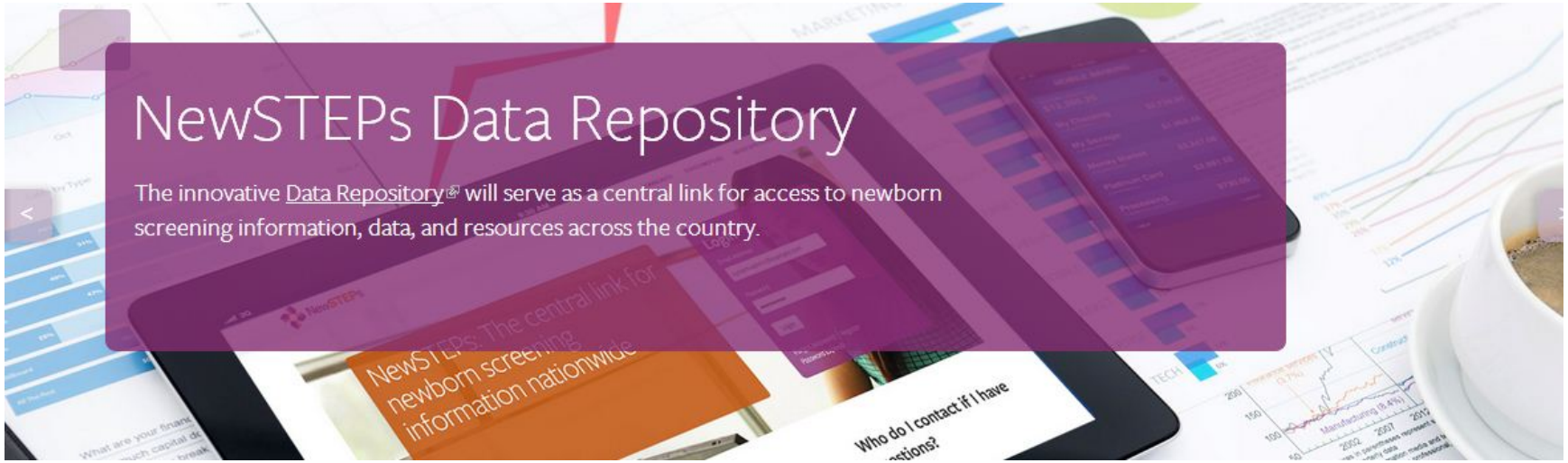
HemoglobinOpathies	
S/S: S,S disease (Sickle cell anemia)	S/β0Th: S, βeta-thalassemia (not on RUSP)
S/β+Th: S, βeta-thalassemia	S/C: S,C disease

Disorders w/Definitions Under Development	
HEAR: Early Hearing Loss	CCHD: Critical Congenital Heart Disease
SCID: Severe Combined Immune Deficiency	HMG: 3-Hydroxy-3-methyglutaric Acidurimia
ßKT: ß-Ketothiolase deficiency	Pompe Disorder
MPS-I: Mucopolysaccharidosis type I	X-ALD: X-Linked Adrenoleukodystrophy

	Classification	Urine Organics or acylglycines	Plasma Acylcarnitines	Mutation analysis	Functional Studies
MCAD	Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
	Definite	Untested or unknown	Untested or unknown	Untested or unknown	Functional fibroblast or Enzyme analysis consistent with MCAD
	Definite	Elevated ***hexanoylglycine***	Elevated: -C8 and -C8>C10 and -C8 >C6 and -C6 and -C10	Untested or unknown	Untested or unknown
	Definite	Untested or unknown	Elevated: -C8 and -C8>C10 and -C8 >C6 and -C6 and -C10	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
	Probable	Untested or unknown	Elevated C8 on repeat testing	1 known disease causing variant and 1 variants of uncertain significance in the same gene (Allele 1 - variant known to be disease causing and Allele 2 - variant of unknown significance)	Untested or unknown
	Probable	Elevated ***hexanoylglycine***	Elevated C8 on repeat testing	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Probable	Untested or unknown	Elevated C8 on repeat testing	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
	Possible	Elevated ***hexanoylglycine***	Elevated C8 on repeat testing	No variants found	Untested or unknown
	Possible	Elevated ***hexanoylglycine***	Untested or unknown	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
	Possible	Elevated ***Hexanoylglycine***	Untested or unknown	No variants found	Untested or unknown
	Possible	Untested or unknown	Elevated C8 on repeat testing	No variants found	Untested or unknown
	Possible or Carrier	Untested or unknown	Elevated C8	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Possible or Carrier	Elevated ***Hexanoylglycine***	Normal	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown

APPLICATION OF CASE DEFINITIONS

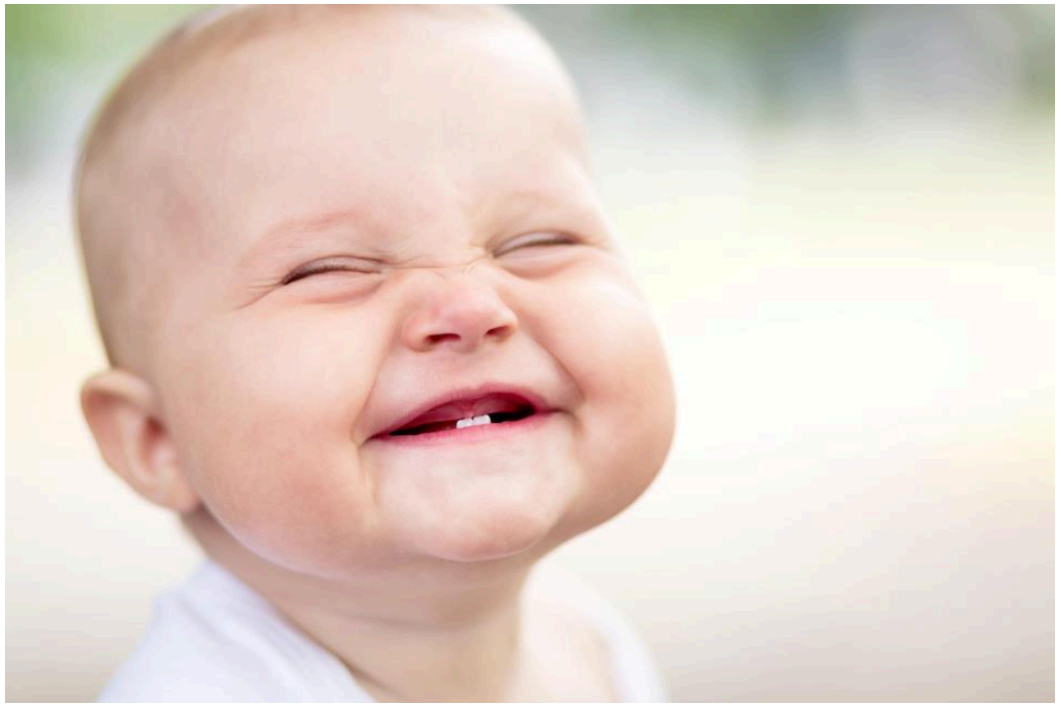
National Data Repository for Newborn Screening



Purpose: Provide tools to state newborn screening systems to adequately evaluate, analyze, and benchmark the performance of their tests and the quality of their newborn screening programs

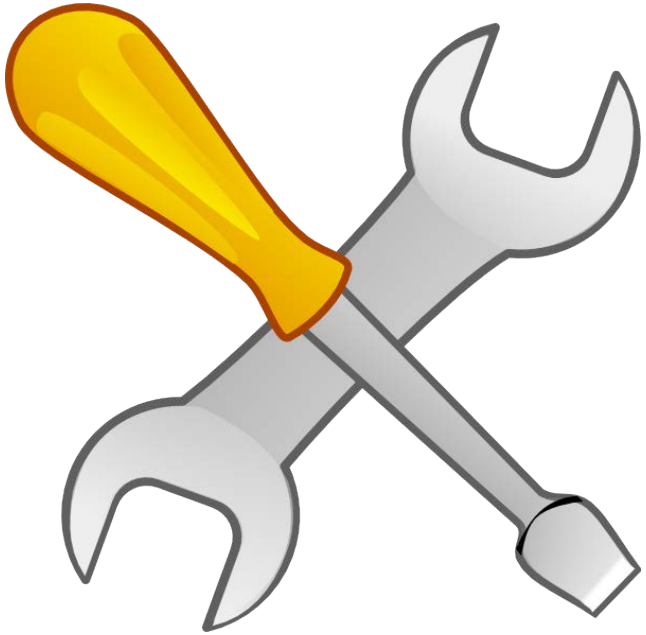
DATA COLLECTION AT THE STATE LEVEL: NEWSTEPS

- Over 4000 cases have been entered by 20 state newborn screening programs
- Data collection:
  - Basic demographic data
  - NBS processes (timeliness, missed cases)
  - Case specific information



TOOLS TO FACILITATE THE IMPLEMENTATION OF CASE DEFINITIONS

- Data import template
- Toolkit
  - Worksheets
  - Tables
  - Letter of introduction to specialists



Available at www.newsteps.org

EVALUATION AND EVOLUTION OF CASE DEFINITIONS

- aggregate data will be shared with the clinical expert teams to assess if the case definitions have performed as anticipated, utilizing measures of data quality, representativeness, and stability.
- comparison of cases reported to NewSTEPs using the case definitions will be compared to and expected frequencies of cases, and through comparison to frequencies reported to clinical registries.
- case definitions will be reviewed every 3 years and modifications to the case definitions will be made, as needed.
- case definitions for new disorders will be developed as they are added to the RUSP.

NEXT STEPS

- Manuscript to be submitted to MMWR following ACHDNC discussion
- Continuing to encourage state participation in data collection
- Utilizing data to calculate frequency of disorders, identify opportunities for improvement

ACKNOWLEDGMENTS

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REGIONAL GENETIC AND NEWBORN SCREENING SERVICES COLLABORATIVES

- Region 1: New England Genetics Collaborative: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont
- Region 2: New York Mid-Atlantic Collaborative: District of Columbia, Delaware, Maryland, New Jersey, New York, Pennsylvania, Virginia, and West Virginia
- Region 3: Southeast Regional Collaborative: Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, Puerto Rico, South Carolina, Tennessee, and U.S. Virgin Islands
- Region 4: Midwest Genetics Collaborative: Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin
- Region 5: Heartland Genetics and Newborn Screening Collaborative Arkansas, Iowa, Kansas, Missouri, Nebraska, North Dakota, Oklahoma, and South Dakota
- Region 6: Mountain States Genetics Regional Collaborative: Arizona, Colorado, Montana, New Mexico, Nevada, Texas, Utah, and Wyoming
- Region 7: Western States Genetic Services Collaborative: Alaska, California, Guam, Hawaii, Idaho, Oregon, and Washington

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