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

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.
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 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.
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 encouraged 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)
PILOTTING 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
- Case Definition Tables for most of the initial RUSP Conditions (26/29)
- Classification tables are posted at [www.newsteps.org](http://www.newsteps.org)
# Metabolic Disorders

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

## Endocrine Disorders

| CH: Primary congenital hypothyroidism |
| CAH: Congenital adrenal hyperplasia |

## Other Disorders

| BIO: Biotinidase deficiency |
| CF: Cystic fibrosis |
| GALT: Classic galactosemia |

## Hemoglobinopathies

| S/S: S,S disease (Sickle cell anemia) |
| S/β+Th: S, βeta-thalassemia |
| S/C: S,C disease |

## Disorders w/Definitions Under Development

| HEAR: Early Hearing Loss |
| SCID: Severe Combined Immune Deficiency |
| βKT: β-Ketothiolase deficiency |
| MPS-I: Mucopolysaccharidosis type I |

<p>| CCHD: Critical Congenital Heart Disease |
| HMG: 3-Hydroxy-3-methylglutaric Aciduria |
| Pompe Disorder |
| X-ALD: X-Linked Adrenoleukodystrophy |</p>
<table>
<thead>
<tr>
<th>Classification</th>
<th>Urine Organics or acylcarnitines</th>
<th>Plasma Acylcarnitines</th>
<th>Mutation analysis</th>
<th>Functional Studies</th>
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</thead>
<tbody>
<tr>
<td>Definite</td>
<td>Untested or unknown</td>
<td>Untested or unknown</td>
<td>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)</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Definite</td>
<td>Untested or unknown</td>
<td>Untested or unknown</td>
<td>Untested or unknown</td>
<td>Functional fibroblast or Enzyme analysis consistent with MCAD</td>
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<tr>
<td>Definite</td>
<td>Elevated <strong>hexanoylglycine</strong></td>
<td>Elevated: -C8 and -C8&gt;C10 and -C8 &gt;C6 and -C6 and -C10</td>
<td>Un tested or unknown</td>
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<tr>
<td>Definite</td>
<td>Untested or unknown</td>
<td>Elevated: -C8 and -C8&gt;C10 and -C8 &gt;C6 and -C6 and -C10</td>
<td>2 variants of uncertain significance in the same gene (predicted to be pathogenic) (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Probable</td>
<td>Untested or unknown</td>
<td>Elevated C8 on repeat testing</td>
<td>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)</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Probable</td>
<td>Elevated <strong>hexanoylglycine</strong></td>
<td>Elevated C8 on repeat testing</td>
<td>1 known disease causing variant (Allele 1 - variant known to be disease causing)</td>
<td>Untested or unknown</td>
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<td>Probable</td>
<td>Untested or unknown</td>
<td>Elevated C8 on repeat testing</td>
<td>2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Possible</td>
<td>Elevated <strong>hexanoylglycine</strong></td>
<td>Elevated C8 on repeat testing</td>
<td>No variants found</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Possible</td>
<td>Elevated <strong>hexanoylglycine</strong></td>
<td>Untested or unknown</td>
<td>2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)</td>
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<tr>
<td>Possible</td>
<td>Elevated <strong>Hexanoyglycine</strong></td>
<td>Untested or unknown</td>
<td>No variants found</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Possible</td>
<td>Untested or unknown</td>
<td>Elevated C8 on repeat testing</td>
<td>No variants found</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Possible or Carrier</td>
<td>Untested or unknown</td>
<td>Elevated C8</td>
<td>1 known disease causing variant (Allele 1 - variant known to be disease causing)</td>
<td>Untested or unknown</td>
</tr>
<tr>
<td>Possible or Carrier</td>
<td>Elevated <strong>Hexanoyglycine</strong></td>
<td>Normal</td>
<td>1 known disease causing variant (Allele 1 - variant known to be disease causing)</td>
<td>Untested or unknown</td>
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</tbody>
</table>
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.
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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- 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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