# Surveillance case definitions for disorders detected by dried blood spot newborn screening

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# The Context for Surveillance Case Definitions

- We have seen an exponential increase in genetic testing and newborn screening.
- We have moved toward uniformity in the NBS panels and performance metrics, BUT diagnoses are often not comparable from practice to practice or between newborn screening programs.
- A need exists to develop a simple and standardized model for nominal categories of disease diagnosis.
- This will allow for harmonization across data systems, programs and patients.

# Legal Imperative

- **Newborn Screening Saves Lives Act 2008**
  - … the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children shall …"consider ways to ensure that all States attain the capacity to screen for the conditions…"
  - "coordination of surveillance activities, including standardized data collection and reporting, harmonization of laboratory definitions for heritable disorders and testing results, and confirmatory testing and verification of positive results, in order to assess and enhance monitoring of newborn diseases…"

# Why a surveillance definition?

- **It is of foremost importance to precisely define what will be considered as a case, in order to:**
  - accurately monitor the trends of reported diseases,
  - detect their unusual occurrences and, consequently,
  - evaluate the effectiveness of intervention.
- **Thus, the usefulness of public health surveillance data depends on its uniformity, simplicity and timeliness.**
- **Necessary as we combine data from multiple sources, or for a state/region to compare**

MMWR October 19, 1990 / Vol. 39 / No. RR-13, “Case Definitions for Public Health Surveillance”

# Surveillance vs. clinical case definition

- Surveillance case definitions are intended to establish uniform criteria for disease reporting;
- They should not be used as sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, providing standards for reimbursement, or initiating public health actions.
- Use of additional clinical, epidemiologic, and laboratory data may enable a physician to diagnose a disease even though the surveillance case definition may not be met.

MMWR October 19, 1990 / Vol. 39 / No. RR-13, “Case Definitions for Public Health Surveillance”

# The Goals of the Initiative

- Develop a model for categorical determination of diagnosis of NBS disorders for public health surveillance
- Refine model to be comprehensive and useful
- Build consensus on case definitions from stakeholder groups
- Present case definitions to the SACHDNC for approval
- If approved by SACHDNC, forward to Secretary HHS for approval and if approved, become standard policy for reporting.

# The Process

- **Convened gatherings of subject matter experts**
  - Hematologists
  - Metabolic Geneticists
  - Pulmonologists
  - Immunologists
  - Endocrinologists
- **Conference calls, face-to-face, web-based interactions**
- **Discuss potential case definition models**
  - Quantitative, tier, diagnostic

# Quantitative Model

| Molecular | Enzymatic | Biochemical/metabolite markers | Clinical presentation | NBS results |
|---|---|---|---|---|
| 7- 2 known disease causing mutations | 5- Zero enzyme activity, consistent with disease | 5- All biomarkers/metabolites present consistent with disorder | 5- Illness consistent with diagnosis | 5- classic elevations or primary and secondary markers for disorder of interest |
| 6- 1 known disease causing mutation and 1 mutation likely to cause disease | 4- Enzyme activity decreased, consistent with disease | 4- Some elevated metabolites that could be consistent with disorder | 4- non-specific presentation | 4- elevation of primary markers |
| 5- 2 mutations suspicious of causing disease | 3- Enzyme activity between carrier and disease levels | 3- Elevation of metabolites, nonspecific for disorder | 3- poor growth or feeding | 3- nonspecific elevation of multiple markers- including secondary markers |
| 4- 1 known mutation & 1 mutation of uncertain significance | 2- Enzyme activity at carrier levels | 1- Normal metabolic testing | 1- no problems | 2- Elevation of secondary markers only |
| 3- 2 mutations of uncertain significance | 1- Enzyme activity between normal and carrier levels | 0- Not done | 0- not known | 1- nonspecific elevation of nonspecific markers |
| 2- 1 known causing mutation found, no other mutation identified | 0- not done | | | 0- no abnormalities |
| 1- 1 mutation of uncertain significance found, no other mutation identified | | | | |
| 0- Not done | | | | |

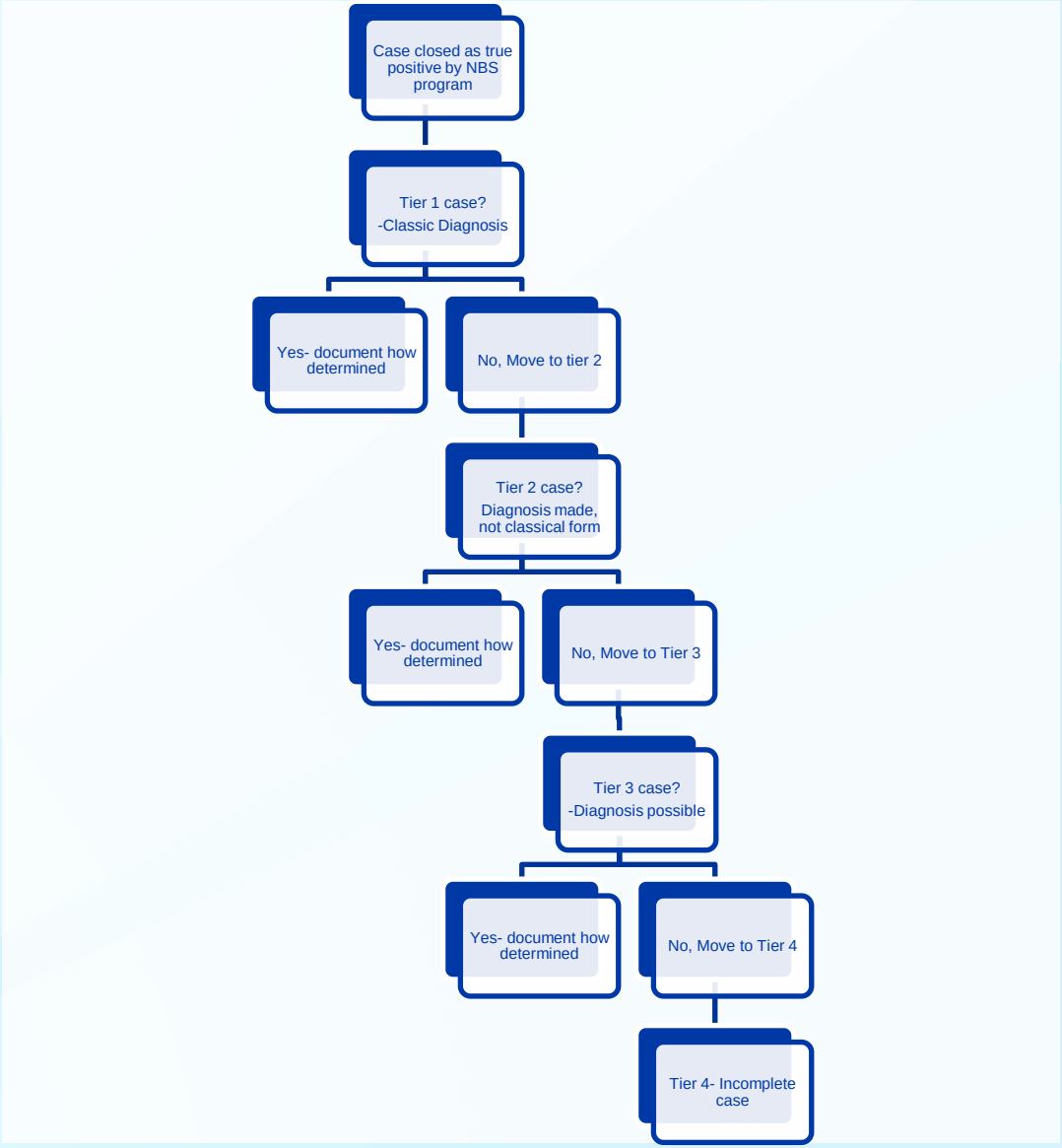
**> 10- Definite diagnosis** **7-10- Probable diagnosis**

**5-7- Possible diagnosis** **<5 Unlikely to be diagnosis**

# Tier Model

First tier would be those cases that no one disputes, everyone agrees is the disease- for instance, Sweat Chloride ≥60 would be agreed upon by all pulmonologists to be classic CF.

A  tier model would separate out the clear cut cases of disease, then focus the quantitative model on those that are more ambiguous and could fall out of true disease or not based on the extent of the workup and those results.



# Diagnostic Model

## (e.g. CDC 4-State pilot, based on NYMAC Diagnostic Guidelines)

| Condition | Definite | Probable/Possible | Not a Case |
|---|---|---|---|
| VLCAD | 2 Pathogenic mutations<br><br>OR<br><br>1 pathogenic mutation + abnormal fibroblast essay<br><br>OR<br><br>Abnormal fibroblast assay + typical VLCAD acycarnitine profile<br><br>Note:<br>If 2 mutations, but no parent studies, accept as case if ACP pattern is consistent | Typical acylcarnitine profile, confirmed on repeat testing | No mutations upon sequencing<br><br>OR<br><br>Normal fibroblast profiling<br><br>OR<br><br>Mild increase of ACP, normal on confirmatory test, no sequencing or fibroblast test |

# Pre-Meeting Work on Wikipage in Response to Draft Models

- 1. What are the strengths and weaknesses of each model?
- 2. What are the major problems/gaps and what are the possible solutions?
- 3. Provide specific case data and apply it to the draft model.
- 4. Is there another model or hybrid model with a different scoring system that could work better. Please add/describe your proposed model.
- 5. Provide specific case data and apply it to your proposed model.
- 6. Describe any gaps and possible solutions.

# Work Sessions

- **Face-to-face June 2011**
  - Classic SCID, Leaky SCID and Omenn Syndrome, Non-SCID Disorders
  - CF
  - Hemoglobinopathies
  - PKU, MSUD, BIOT, HCY, GALT, MCAD, 3MCC, ARG1Def
- **Endocrinology group met by conference call Fall 2011**
- **Metabolic group met face-to-face February 2012 to complete**

## Case Definitions for the Hemoglobinopathies on the RUSP

| Diagnosis | NBS result | Tier 1: Definite | Tier 2: Probable | Tier 3: Possible | Tier 4: Incomplete |
|---|---|---|---|---|---|
| Double heterozygote (e.g., FSC) | | Two independent linked samples using complementary methods:<br>1) IEF or HPLC<br>AND<br>2) quantitative HPLC or DNA-based methods (genotyping) | Two independent linked samples using qualitative complementary methods OR one sample plus family studies | • Family history and one sample (NBS) or<br>• lab confirmation on same sample | • Diagnosis: Dx without testing including no NBS (e.g., ICD)<br>• Missing data<br>• Only NBS |
| Homozygous (e.g.,FS) | | Two independent linked samples using complementary methods and:<br>• "complete genotyping" or a DNA method that rules out HPFH OR<br>• DNA and family studies (quantitative hb separation and CBC on both biological parents) | Two independent linked samples using qualitative complementary methods WITH incomplete genotyping. or One sample (DBS) plus family studies. | • First sample NBS plus age-specific MCV (WNL) or<br>• Family history and DBS if low MCV and alpha thal genotyping<br>• MCV: age and alpha-thal genotyping<br>• Decreased MCV:age and Barts<br>• Decreased MCV:age with others:<br>▪ Alpha or beta thal<br>▪ Ss and alpha thal<br>▪ S beta and no thal<br>• S or c alpha<br>NOTE: NEEd algorithm. Need to break this row into multiple rows. Overlap with beta and alpha thal. | • Diagnosis: Dx without testing including no NBS (e.g., ICD)<br>• Missing data<br>• Only NBS |

Scoring:

- 7 → Definitive Diagnosis
- 4 to 6 → Possible Diagnosis
- 0 to 3 → No SCID
- <0 → Possible DiGeorge

# SCID

| Points | Clinical | Lymphopenia | Lymph. Function | Molecular |
|---|---|---|---|---|
| 7 | | Absent T cells (<-3 SD for age) | No T cell prolif to mitogens (<10% control) | 2 known disease causing mutations or 1 on X or 22 |
| 6 | GVHD-like rash | Any degree of lymphopenia (inc. normal) + mat engraft | | 1 known and one likely |
| 5 | Failure to thrive, Fevers, Opportunistic infection e.g. pneumocystis, vaccine-strain rotavirus, BCG or others | Any degree of lymphopenia + abnormal RA/RO ratio | | 2 suspicious |
| 4 | | | | 1 known and 1 uncertain |
| 3 | | lymphopenia < -2 SD for age, but not absent | | 2 uncertain |
| 2 | Serious systemic bacterial infection (meningitis) or Severe CMV, adenovirus or influenza | | | 1 known only |
| 1 | | | Proliferation only to mitogens, not antigens | 1 uncertain only |
| 0 | | lymphocytes > -2 SD for age (autologous) | Proliferation to mitogens and antigens | Not performed |
| <0 | Presence of clinical features consistent with DiGeorge anomaly | | | |

**Category definitions:**

I. CF

Hypertrypsinogenemia[5] and sweat chloride concentration ≥ 60 mmol/L (regardless of age) and/or detection of **two** *in trans*[6] CF disease-causing mutations[2].

II. CRMS (CF-related metabolic syndrome), or CRD (CFTR[4]-related disorder) (these infants may be re-categorized over time as described in the Overview above and Figure 1).

A. CRMS - An asymptomatic, hypertrypsinogenemic[5] infant with either:

- A sweat chloride concentration 30-59 mmol/L if age < 6 months or 40-59 mmol/L if age ≥ 6 months on at least two occasions (recommended sweat chloride testing schedule: 1st test by two weeks of age, 2nd by two months, 3rd at 6 months) and completed EGA[3] with **fewer than two** CF disease-causing mutations[2] OR
- A sweat chloride concentration <30 mmol/L if age < 6 months or <40 mmol/L if age ≥ 6 months and **two** CFTR mutations, *in trans*[6], of which **no more than one** is known to be CF disease-causing.
- If genetic testing has revealed 2 heterozygous (different) mutations, then additional family evaluation (phase testing) should be performed to confirm that the mutations are *in trans*.

## Case Definitions for the Endocrinology Conditions on the RUSP

### Primary Congenital Hypothyroidism (CH)

| Diagnosis | Definite | Probable | Possible | Incomplete |
|---|---|---|---|---|
| Primary congenital hypothyroidism* | TSH > 10 mU/L and free T4 or total T4 < age established reference range on serum testing$^{\Delta}$ at start of treatment | TSH > 10 mU/L and normal or no free T4/total T4 on serum testing$^{\Delta}$ at start of treatment | TSH 6-10 mU/L and low, normal, or no free T4/total T4 on serum testing$^{\Delta}$ at start of treatment | NBS only, no follow-up tests |
| Central (Secondary) congenital hypothyroidism | TSH < 10 and free T4 < age established reference range on serum testing$^{\Delta}$ at start of treatment, with documentation of other pituitary hormone deficiencies or midline defects. | TSH < 10 and free T4 < age established reference range on serum testing$^{\Delta}$ at start of treatment, with no other pituitary hormone deficiencies or midline defects. | | |
| TBG or other low binding protein defects | Free T4 normal, total T4 low, TSH normal, TBG low | | | |

*This should be considered provisional until diagnosis confirmed by three years of age either by TSH rise or retesting off treatment at three years of age

$^{\Delta}$ Repeat confirmatory DBS testing acceptable if serum testing unavailable.

| Condition | Definite | Probable | Possible | Incomplete | Comment |
|---|---|---|---|---|---|
| Glutaric acidemia type I | Plasma acylcarnitine profile -Elevated C5-DC and urine or serum elevation of glutaric and 3-OH glutaric<br>OR 2 disease causing mutation OR confirmatory enzyme activity | Plasma acylcarnitine profile -Elevated C5-DC – elevated 3-OH glutaric without glutaric and 2 variants OR 1 variant and 1 disease causing mutations | Plasma acylcarnitine profile -Elevated C5-DC – indeterminant UOA and 1 disease causing mutation | Plasma acylcarnitine profile -Elevated C5-DC | |
| VLCAD | two disease causing mutations, preferably confirmed in trans, OR<br>one disease causing VLCAD mutations | One known disease causing mutation and persistent acylcarnitine profiles with isolated C14:1 elevation | persistent acylcarnitine profiles with isolated C14:1 elevation<br>carnitine | Increase of C14:1, normal on confirmatory test, with no sequencing or fibroblast testing | |
| | with abnormal fibroblast assay OR<br>In the absence of DNA sequencing, abnormal fibroblast assay with plasma acylcarnitine consistent with VLCAD profile pattern (including increased C14:1) | acylcarnitine profile consistent with VLCAD profile (including C14:1), confirmed on repeat testing | | | |

# Next Steps

- **Share through the regional collaboratives**
  - Feedback due to HRSA by May 31, 2012
- **Pilot testing of definitions through APHL**
- **Presentation of definitions to SACHDNC**
  - If approved, submitted to HHS for approval
- **National use for surveillance of NBS disorders**
- **Share internationally, other public health organizations (in process)**
  - New Zealand, Australia, International Society of Neonatal Screening

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