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

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Follow-Up Workshop: "Data Harmonization"

The Context

- We have seen an exponential increase in genetic testing and newborn screening.
- While there is a movement toward uniformity in the newborn screening panels and performance metrics, 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…"*

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"

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"

The Goals

- Develop a model for categorical determination of diagnosis for public health surveillance
- Refine model to be comprehensive and useful for all newborn screening disorders to date
- Get consensus on case definitions from stakeholder groups
- Will be presented to the SACHDNC for approval
- If approved by SACHDNC, will go forward to Secretary HHS for approval and if approved, become standard policy for reporting.

In other words, “saddle up.”

The Process to Date

- **Convene a meeting of subject matter experts**
  - *Hemoglobinology*
  - *Metabolic*
  - *Pulmonology*
  - *Immunology*
  - *Endocrinology (Fall 2011)*
- **Conduct pre-meeting conference calls and pre-work**
- **Meet in Washington, DC**
  - *June 6, 2011*
  - *HRSA-supported*

Draft Model #1: Quantitative

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

Pre-Meeting Work on Wikipage

- 1. What are the strengths and weaknesses of this 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. (You can add tables to this page or can upload a word document.)
- 5. Provide specific case data and apply it to your proposed model.
- 6. Describe any gaps and possible solutions.

Model #2: Diagnostic criteria

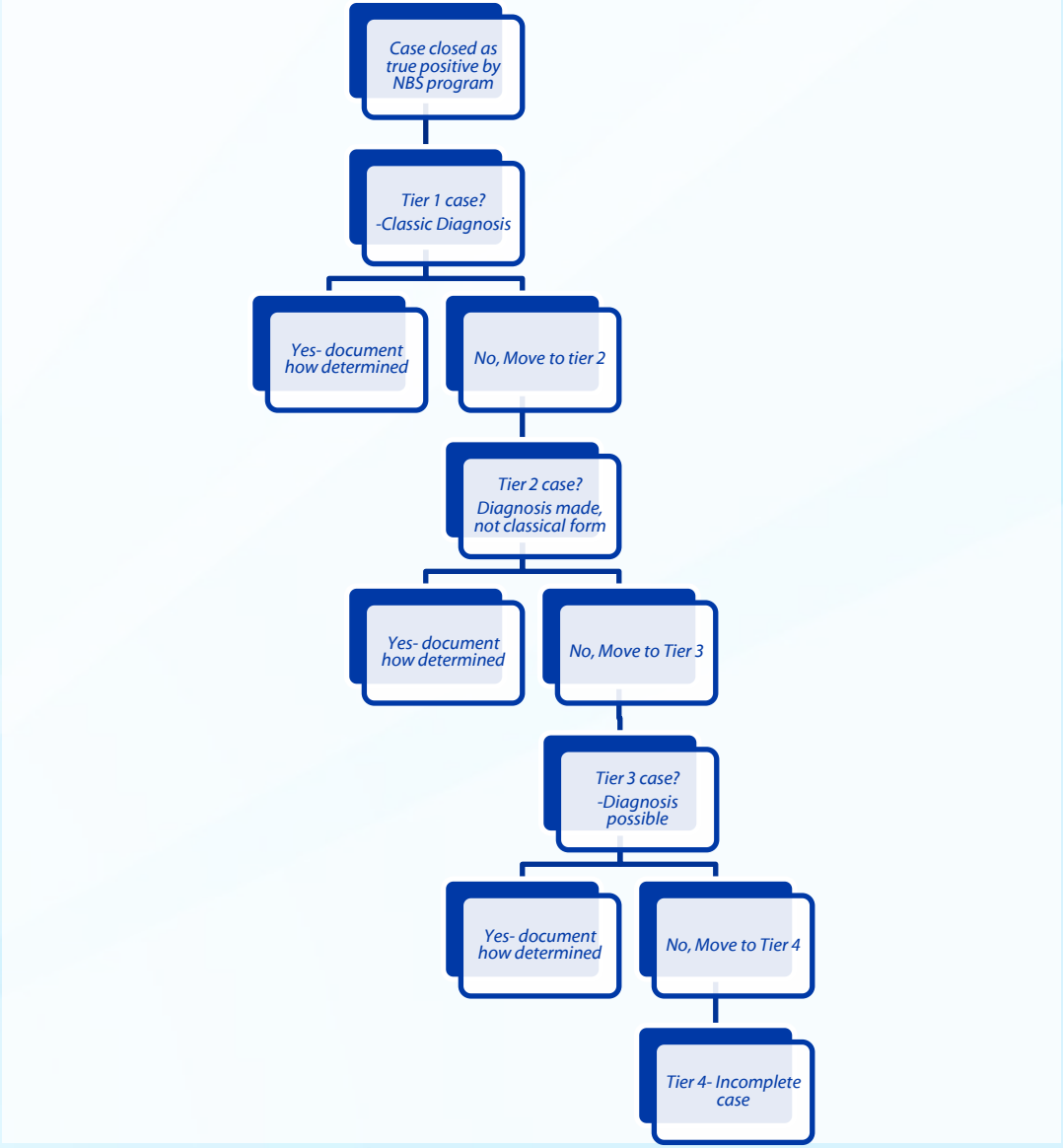
CDC 4-State pilot, based on NYMAC Diagnostic Guidelines

Condition	Definite	Probable/Possible	Not a Case
VLCAD	*2 Pathogenic mutations* *OR* *1 pathogenic mutation + abnormal fibroblast essay* *OR* *Abnormal fibroblast assay + typical VLCAD acycarnitine profile* *Note:* *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* *OR* *Normal fibroblast profiling* *OR* *Mild increase of ACP, normal on confirmatory test, no sequencing or fibroblast test*

Draft Model #3: 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.



Face-to-Face Work Day

- **Goal for subject matters experts to draft surveillance models by end of day**
- **Present progress to group at end of day**
- **Overall, the day was a success**
  - *Classic SCID, Leaky SCID and Omenn Syndrome, Non-SCID Disorders (Quantitative Model)*
  - *CF (Tier Model)*
  - *Hemoglobinopathies (Quantitative), still working issues with variants*
  - *PKU, MSUD, BIOT, HCY, GALT, MCAD, 3MCC, ARG1Def (Diagnostic Model). All the rest left to go.*

Next Steps

- Endocrinology group has recently started working on case definitions
- Need to finish Metabolic disorders
- Share through the regional collaboratives
  - *Feedback*
- Pilot testing of definitions
- Presentation to SACHDNC
  - *If approved, submitted to HHS for approval*
- National use for surveillance of NBS disorders
- Share internationally, other public health organizations

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