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Overview of Cutoff Determinations and Risk Assessment Methods used in Dried Blood Spot Newborn Screening

Presentation to the Advisory Committee on Heritable Disorders in Newborns and Children

February 8, 2018

Joseph Orsini, Ph.D.

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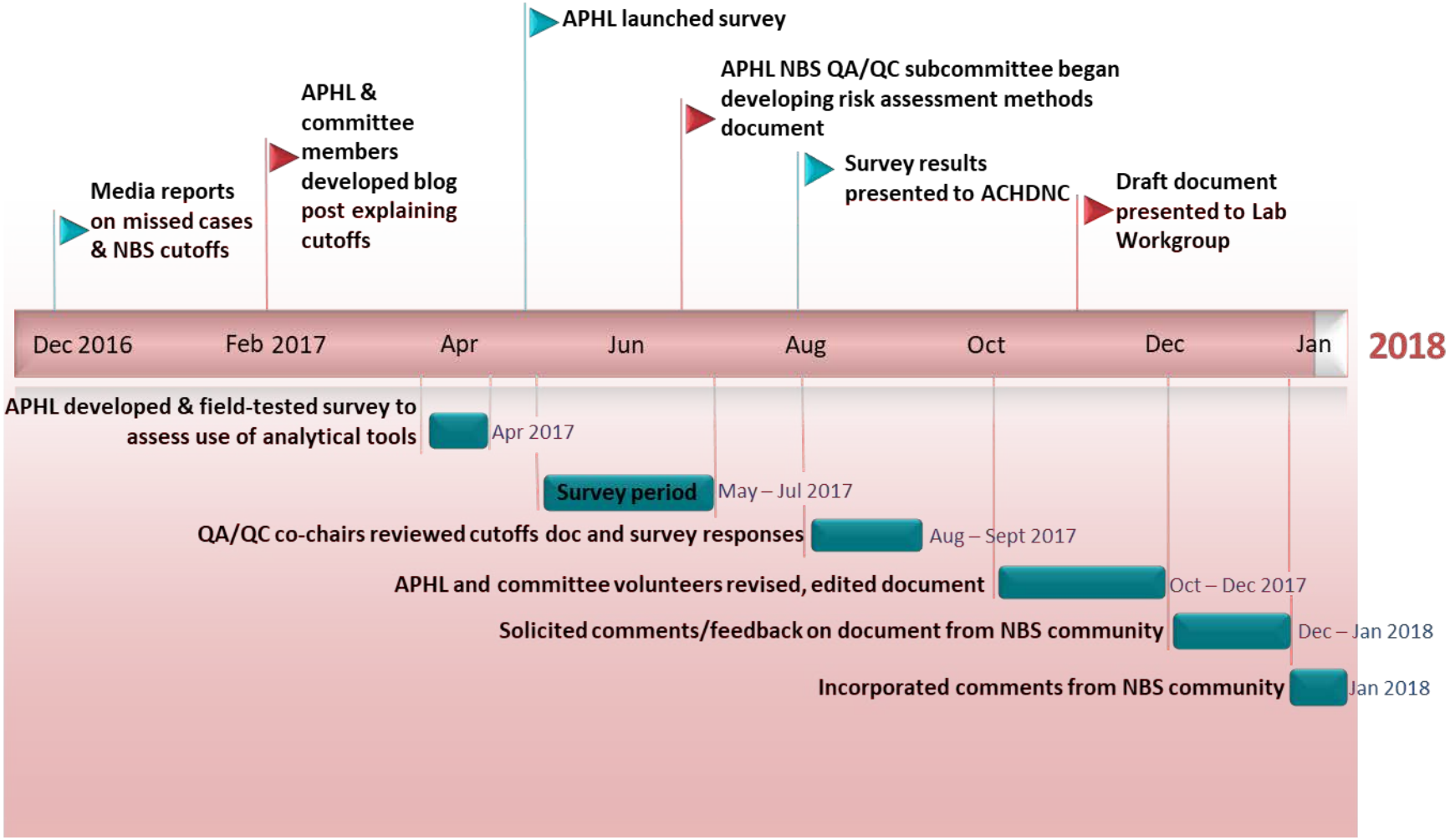
Background


APHL launched survey
APHL NBS QA/QC subcommittee began developing risk assessment methods document
APHL & committee members developed blog post explaining cutoffs
Survey results presented to ACHDNC
Draft document presented to Lab Workgroup
Media reports on missed cases & NBS cutoffs
Dec 2016
Feb 2017
Apr
Jun
Aug
Oct
Dec
Jan
2018
APHL developed & field-tested survey to assess use of analytical tools
Apr 2017
Survey period
May – Jul 2017
QA/QC co-chairs reviewed cutoffs doc and survey responses
Aug – Sept 2017
APHL and committee volunteers revised, edited document
Oct – Dec 2017
Solicited comments/feedback on document from NBS community
Dec – Jan 2018
Incorporated comments from NBS community
Jan 2018

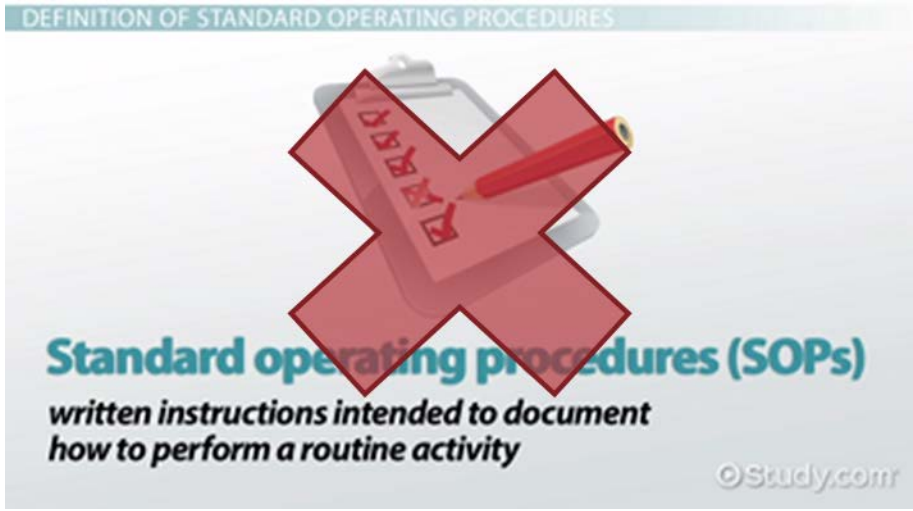
Purpose

- Intended audience: staff of state NBS programs.

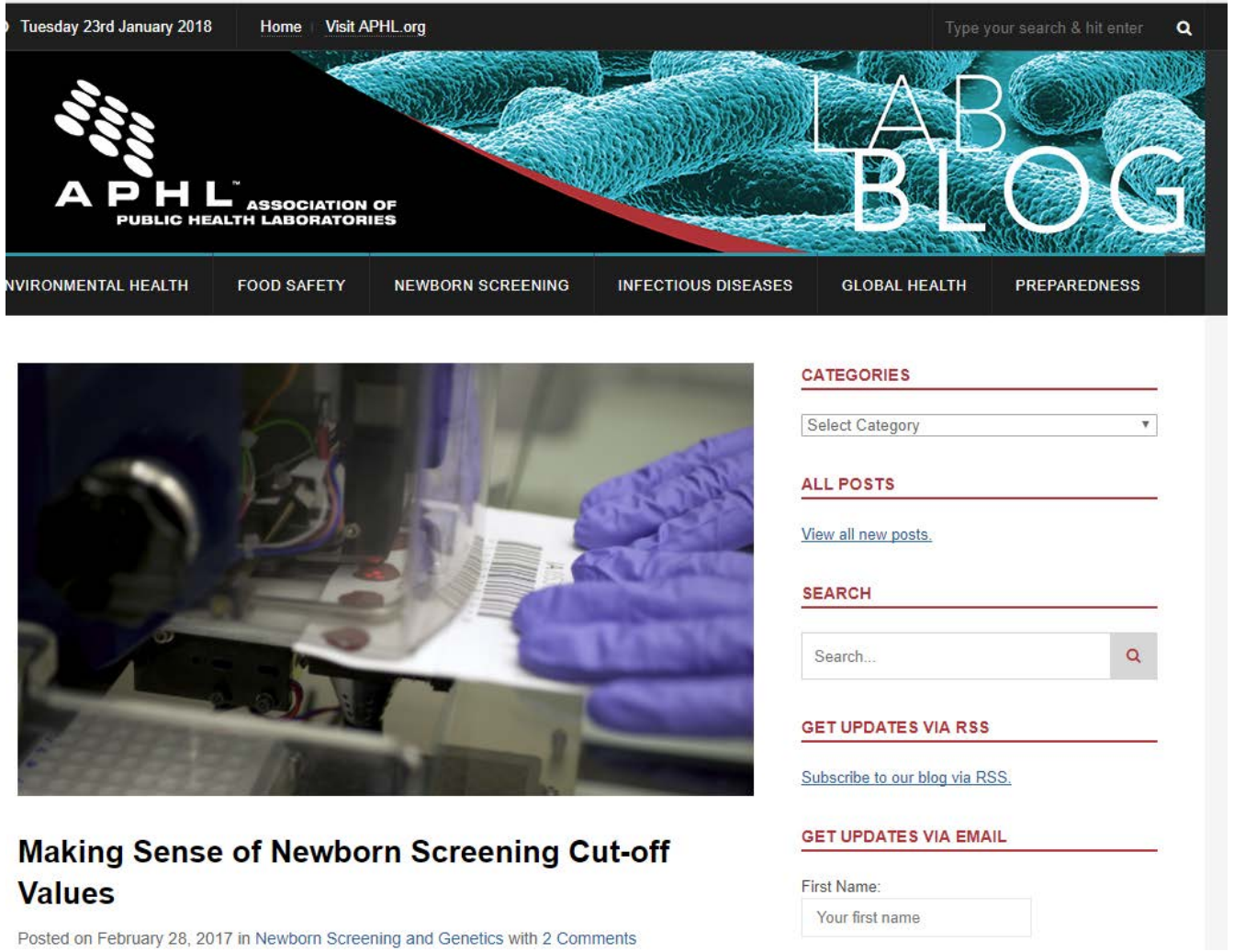
- Assumptions: strong understanding of NBS laboratory methodologies and risk determination.

Purpose (continued)

- Not meant to provide detailed instructions on performing risk assessment in newborn screening.
- Historical and current approaches that laboratories rely on for risk assessment are described, as well as factors that should be considered when establishing and evaluating risk.



For a primer on NBS risk assessment…



Limitations of NBS risk assessment

- NBS is not meant to establish diagnosis.
- Abnormal biomarker levels, identified through screening and evaluated using cutoffs, only indicate that a newborn may be at higher risk for a screened disorder.

Limitations of NBS risk assessment

- For symptomatic newborns or those with family history of a disease, additional diagnostic testing is necessary regardless of the NBS result.
- Regardless of the algorithm used to determine infants at highest risk, NBS may not detect all affected newborns.

Overview of cutoff determination

Conduct a population study

- Hundreds to thousands of specimens
- DBS from unaffected newborns and manufactured controls

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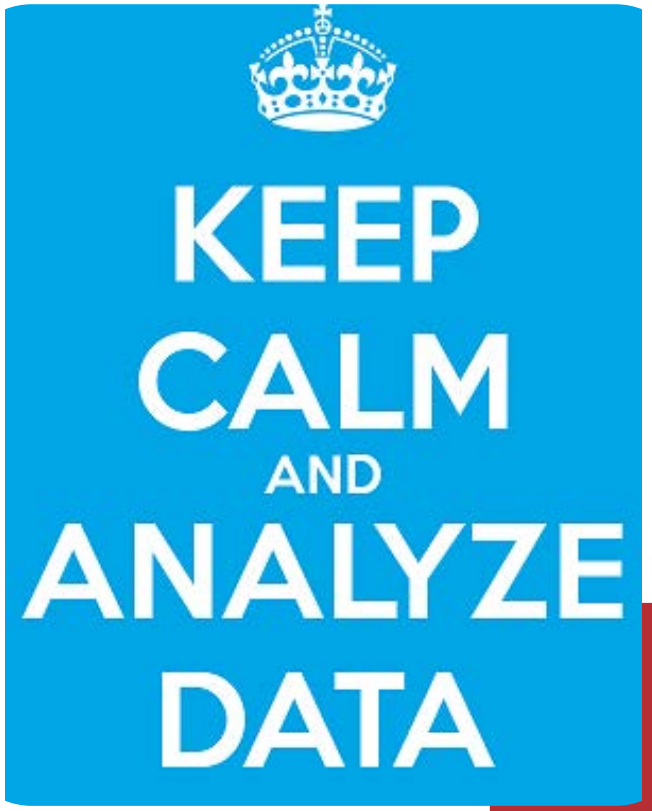

Analyze data, determine preliminary cutoff

- Is method adequately precise to differentiate results close to cutoff?
- For qualitative test, determine %age of results identified as normal/abnormal before setting preliminary cutoff

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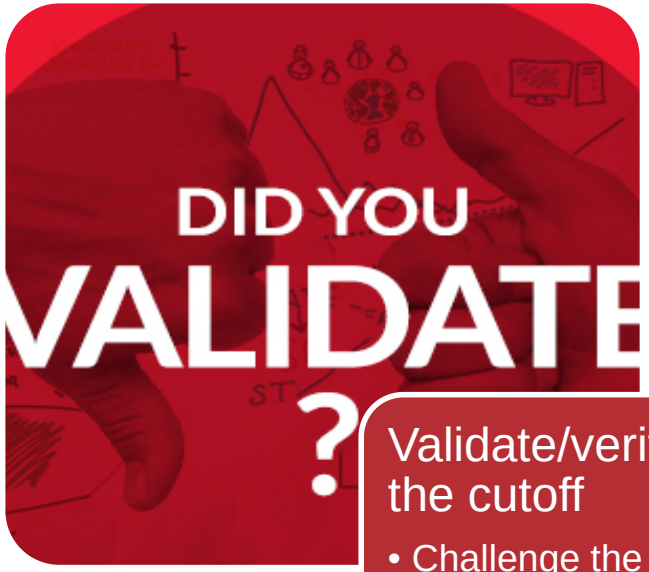
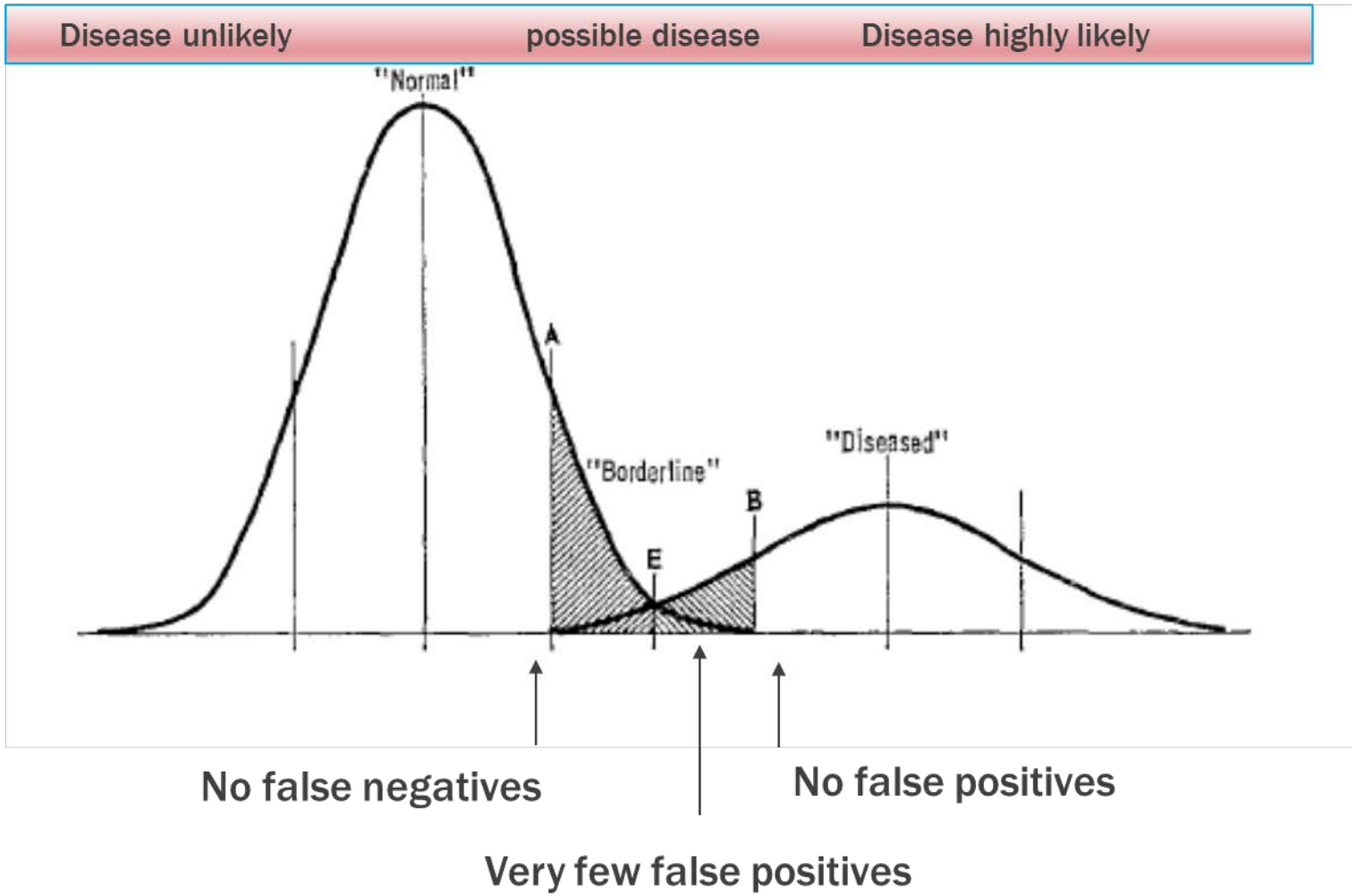


Validate/verify the cutoff

- Challenge the preliminary cutoff
- Compare the cutoff
- Conduct lit search
- Evaluate results of population study
- Set the cutoff

Typical Distribution and cutoffs

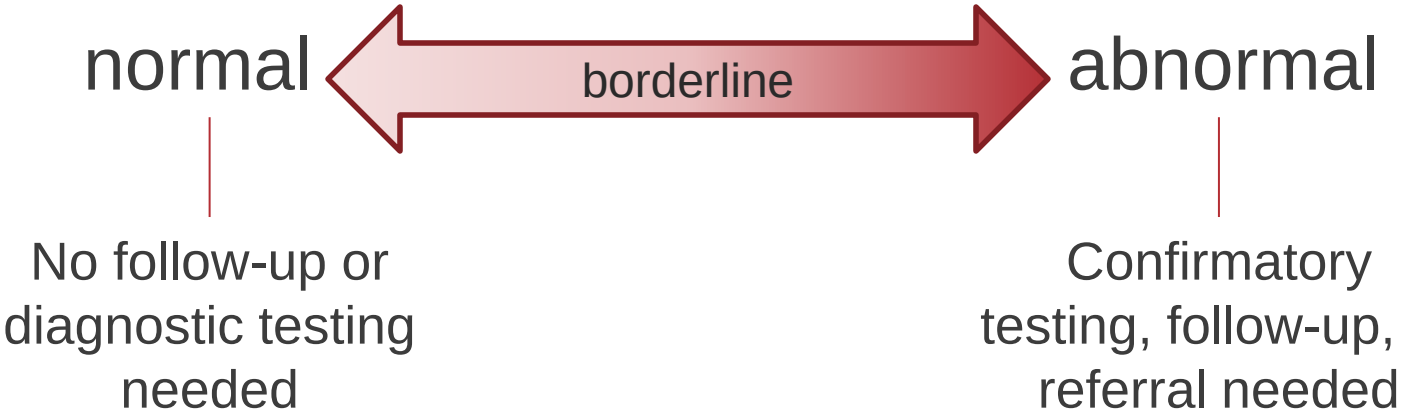


Special Considerations:
Fixed Cutoffs *vs.* Floating Cutoffs

- Generally used for assays that directly measure biomarker concentrations (eg, phenylalanine detected by MS/MS).
- Best to use for assays unaffected by day-to-day or lot-to-lot variability

- Generally used for functional assays that rely on enzyme reaction or antibody-antigen binding; biomarker is not directly measured by instrument
- Use % daily mean or median if assay exhibits day-to-day variability

Special Considerations: Borderline cutoffs



- Specimens found in the borderline range prompt request for 2nd specimen rather than referring the newborn for follow-up diagnostic testing.
- Borderline cutoffs are helpful when biomarker concentration may increase or decrease depending on newborn's age at time of specimen collection, or if marker tends to be elevated at birth due to stress on the newborn resulting from the birthing process (such as 17-OHP).

But wait there's more! (Special Considerations)

- Multiple of the Median (MoM)
  - Similar to fixed cutoff
  - Assumes population median for the marker is constant
  - Result is reported as a multiple of the normal population median rather than biomarker concentration value
  - allows lab to monitor population assay performance by monitoring the median; update the median value used in calculation of patient's result while comparing result to a fixed MoM

Collaborative Laboratory Integrated Reports (CLIR) Functionalities

- **Covariate adjustment**
  - Analytes and ratios are adjusted for demographic variables (e.g., birth weight and age at sample collection).
  - Sex differences are assessed; further adjustments applied if needed.
- **Location harmonization**
  - Allows direct comparison of data for markers across contributing labs.
- **Global contribution of diagnosed case data**
  - Results in a compilation of positive cases to help determine the distribution of markers in the affected population.
- **Large database of normal profiles**
  - Allows incorporation of new tools and/or new analyte combinations so the normal distribution can be evaluated on existing data.

Collaborative Laboratory Integrated Reports (CLIR) Considerations

- **Access is conditional based on contribution of data**
  - Some states have laws/limitations around uses of NBS data that will prevent them from contributing data (hence preventing access).
- **Need to customize algorithm for each state**
  - Not all states screen for the same set of analytes.
- **Better integration needed with LIMS and reporting of results**
- **Variability in case definitions**
  - The tool depends on data entered by individual users; and there can be variability in cases definitions across varied NBS Programs. Not a problem unique to CLIR.

Disorder specific cutoff considerations

- Endocrine Disorders
  - Congenital hypothyroidism
  - Congenital adrenal hyperplasia
- Cystic Fibrosis
- Hemoglobinopathies
- Enzyme Deficiency Disorders
  - Galactosemia
  - Biotinidase deficiency
  - Lysosomal storage disorders (LSDs)
- Amino Acid, Fatty Acid Oxidation,Organic Acid Disorders
- SCID
- X-ALD

Monitoring and Evaluation of Risk Assessment

- Monitor the cutoff:
  - For first 6 months by evaluating test sensitivity, specificity
  - Is incidence and rate of false positives as expected for state population?
  - Every 6 months after routine screening begins
- Reevaluate the cutoff:
  - After kit changes
  - After equipment changes
  - After modifications in testing
  - After learning of false negative cases
  - After learning new clinical information/natural history of disease

Summary

- The document provides an overview of the currently used risk assessment methods.
- It provides a general approach to how to set up a risk assessment.
- Includes an extensive list of the variables that should be considered.
- Is a reference document that can be used for experienced and inexperienced newborn screening scientists.

Acknowledgments

APHL QA/QC Subcommittee Members:

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