RISK ASSESSMENT IN NEWBORN SCREENING

August 2, 2018

Kellie Kelm, PhD, Chair of the Laboratory Standards and Procedures Workgroup

July 30th Workgroup Meeting Agenda

TOPIC	PRESENTER
Welcome and Roll Call (5 min)	Kellie Kelm Susan Tanksley
NBS Risk Assessment and Cutoffs (30 min) • APHL Risk Assessment Guidance Document	Guisou Zarbalian APHL
CDC Quality Assurance Program (30 min) • Harmonization of newborn screening assays	Carla Cuthbert CDC
Newborn Screening Technical Assistance Center and Data Repository (30 min) • Technical assistance site visits and risk assessments	Jelili Ojodu APHL
Future directions (15 min) • Translating information for parents and the public – possible collaboration with Education and Training Workgroup	Susan Tanksley
Wrap-up/Next Steps (10 min)	Kellie Kelm Susan Tanksley

Committee discussions on cut-offs

Feb, May, Aug 2017 presentations at ACHDNC meetings

- February – Michele Caggana (NY), John Thompson (WA), Carol Johnson (IA)
- May – Michele Caggana (NY), Scott Shone (NJ), Amy Gaviglio (MN), also R4S and CLIR tools by Piero Rinaldo (Mayo Clinic) and CDC's NBS QA/QC Program by Carla Cuthbert (CDC)
- August – Susan Tanksley (APHL)

August – outline presented to the workgroup

APHL presentation on Risk Assessment document to the Workgroup

1. November – draft document provided for review
   - Workgroup provided feedback on both dates
2. Document provided widely to newborn screening community in January
   - Most of workgroup's suggestions were addressed in the document
3. Workgroup provided recommended clarifications to first author, Joe Orsini

Workgroup discussion and conclusions on APHL document:

1. The document describes the scientific process behind establishing and validating cut-offs.
2. The document will be valuable to state newborn screening programs.
3. APHL intends for this to be a living document and will revise the document over time.
4. It does not include best practices for screening for all conditions.
5. It does not harmonize newborn screening tests across states.

Committee discussions on APHL Risk Assessment Document

February 2018 – presentation of current draft by Joe Orsini to the committee.

- The Committee decided a vote was not required, acknowledged the document's value and recommended that APHL continue to refine and improve it.
- It was also agreed that that the Laboratory Standards and Procedures Workgroup should focus on what could be done to address public access issues and better ways to collect and store data on false positive results.

August 2018 – final document provided to workgroup and committee.

Changes to the APHL document:

Per feedback from the Advisory Committee, a summary table was added – highlights were pulled from the text of the document to create the table.

QA/QC Subcommittee workgroup consulted with experts in the field on the different methodologies and updated the document to reflect more accurate information.

Method	Use for	Functionalities	Considerations
Fixed cutoff	Assays that directly measure biomarker level	Simplest to establish and apply; simplest for reporting purposes. Fixed cutoffs work best for markers with little birthweight or age dependencies and minimal lot-to-lot or seasonal variability.	Requires regular monitoring to determine if cutoff adjustment or instrument adjustment is needed. Difficult to compare directly with other screening laboratories due to method or instrument differences
Floating cutoff	Assays that show daily variability, or assays that do not directly measure biomarker level (eg, assay depends on binding of enzyme to substrate)	Can be used alone or in conjunction with a fixed cutoff. Produces relatively consistent screen-positive rates. Less prone to fluctuations; less frequent need to adjust cutoff based on assay variability and population mean/median.	Consider removing results from outlier specimens within batch to avoid skewing floating cutoff. Consider number of specimens within batch when using this method. Complicates STAT specimen analysis, as generally the specimens are treated as a batch.

Current status:

Document is close to final draft.

This will be a “living document” and will have changes made in the future.

APHL plans to post it on their website in the near future.

CDC's Quality Assurance and Harmonization Activities

Normalization of NBS Laboratory MS/MS Biomarker Results

Update

Kostas Petritis, PhD

Chief, Biochemical Mass Spectrometry Laboratory

Newborn Screening and Molecular Biology Branch

Teleconference with the Laboratory Standards and Procedures Workgroup Subcommittee

July 30 2018

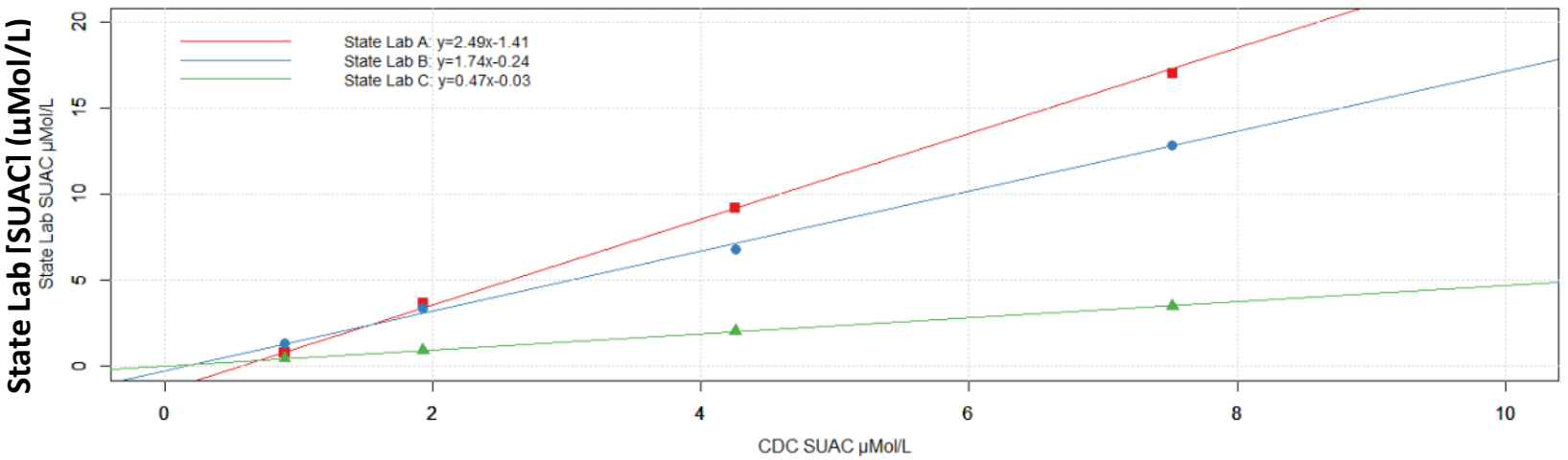
MS/MS Biomarker Measurements and Cutoffs Can Vary Significantly Among Different Labs

>70% (23/32) of RUSP bloodspot disorders can be screened by MS/MS

MS/MS analyte results and cutoff values vary due to:	
Major Contributors	• Extraction methodologies • Derivatized vs. non-derivatized • Few labs account for analyte recovery, most labs do not • Use of additional/different analytes per disorder or second-tier screening
Other Factors	• Population tested • Instrumentation • Internal standards • Calibration techniques

RUSP: Recommended Uniform Screening Panel

Addressing Succinylacetone (SUAC) Lab-to-Lab Variability by Normalizing Results



- ❑ Use QCs to normalize
- ❑ Use PTs to validate the normalization worked

Expectation:

- NBS labs receive the same PT specimens
- PT analytical results should be the same

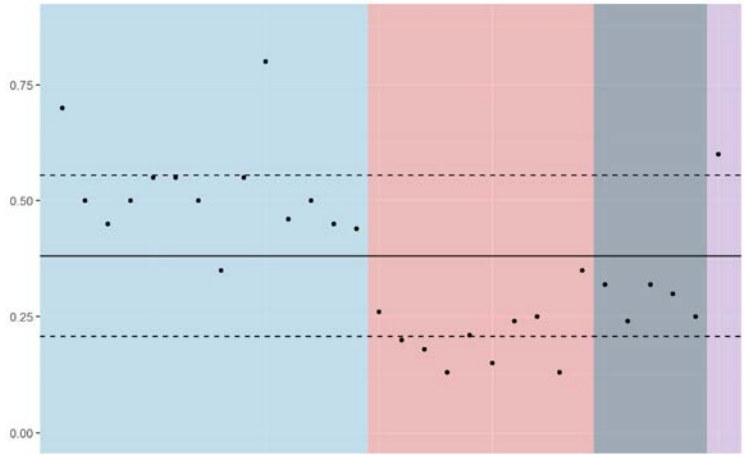
Methods:

- FIA-MS/MS results
- PT specimens are analyzed only once
- QC and PT results from US Q3 2016 event

Concentrations at µmol/L, SUAC: Succinylacetone, PT: Proficiency Test, FIA: Flow Injection Analysis

Normalization of MS/MS results allows the normalization of cutoffs

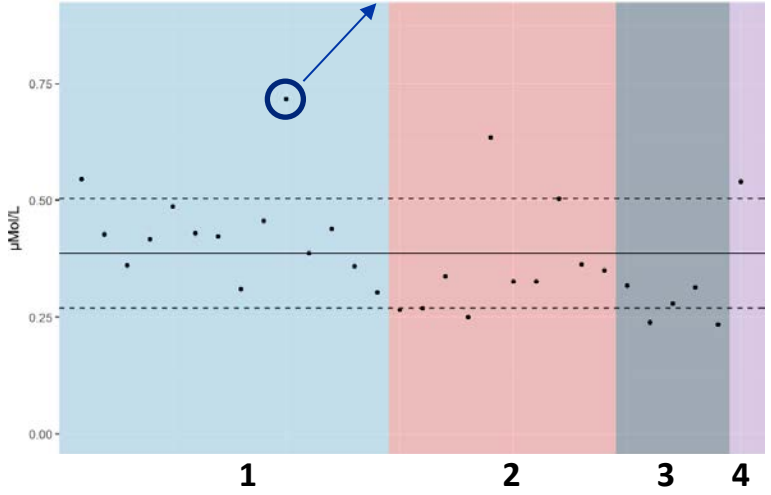
Glutarylcarnitine (C5DC) US labs cutoffs
Without normalization … CV: 45.55%



Method Platform

Glutarylcarnitine (C5DC) US labs cutoffs
After normalization … CV: 30.22%

NBS labs with high biomarker normalized cutoffs could reevaluate them



Method Platform

C5DC: Glutarylcarnitine, CV: Coefficient of Variation, PT: Proficiency Test

WHAT'S NEW…

Building a web interface for visualizing the normalization results
Lab specific, in design phase

Considerations and Resolutions

1) You can not normalize for analytes not included in the CDC QC materials
   - Adding more analytes in our Amino Acid and Acylcarnitines (AAAC) QC materials.
   - Current production (shipping January 2019) will contain those additional analytes:
     - Creatine (CRE)
     - Guanidine Acetic Acid (GAA)
     - Creatinine (CRN)
     - C26:0-lysophosphatidylcholine (C26-LPC)
     - C24:0-lysophosphatidylcholine (C24-LPC)
     - C22:0-lysophosphatidylcholine (C22-LPC)
     - C20:0-lysophosphatidylcholine (C20-LPC)
     - Tiglyl carnitine (C5:1)
     - Tetradecenoyl carnitine (C14:1)
   - More analytes to be added in the future (considering ASA, C12:1, C14:2, ADO, dADO etc…)

Considerations and Resolutions

2) Using PTs to confirm that the normalization worked adequate for a proof of concept study but not a long term solution as:

- ❑ Only one measurement
- ❑ Not all analytes are enriched in every PT event
- ❑ Some PT analytes outside the dynamic range of our QC materials (SUAC, Leu, Tyr for Q3 2016)

    - Considering the creation of an additional QC specimen with all analytes set at CDC cutoffs (average of all US cutoffs) to be used for normalization validation

NewSTEPs

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QUALITY IMPROVEMENT

Jelili Ojodu, MPH
Director, Newborn Screening & Genetics
Association of Public Health Laboratories

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GOAL 1:
COMMUNICATION & OUTREACH

Strengthening the newborn screening system through:

- ✓ Enhancement of the existing network of stakeholders by creating a **culture of trust,**
- ✓ providing opportunities for **timely & interactive communication**, and
- ✓ offering a **forum for collaboration** among national, regional and state NBS programs.

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GOAL 2:

DATA

Continuous quality improvement and data-driven outcome assessments in the NBS system by providing:

- ✓ Standardized **data repository,**
- ✓ dynamic data **infographics** and **visualization** tools, and by
- ✓ supporting integration of health information technology (**HIT**) frameworks including **HL7 messaging.**

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GOAL 3:

TECHNICAL ASSISTANCE

Create dynamic national NBS TA resource center that proactively:

- ✓ Provides **training**,
- ✓ **addresses challenges**, and
- ✓ supports **program improvement**

QUALITY IMPROVEMENT ACTIVITIES:

- **COMPREHENSIVE SITE REVIEWS**
- **FOCUSED SITE REVIEWS**
  - **ESTABLISHING/REVIEWING CUT-OFFS**
  - **EXPERTS IN LABORATORY AND FOLLOW-UP**

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Quality Improvement Funding

Cooperative Agreement #UG8MC31893

- Recently awarded (September 1, 2018 start date)
- Proposed Activities
  - Facilitate quality improvement projects (via technical assistance, direct funding) for five focus areas:
    1. Reporting NBS results in a timely manner
    2. **Identification of, and follow-up on, out-of-range results**
    3. Processes for communication of NBS results to providers and families
    4. Processes for confirming diagnosis
    5. Emerging issues that may impact quality, accuracy or timeliness of NBS

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Other Activities (CDC Funded)

- NBS QA/QC Subcommittee
  - Educational webinars
    - New conditions
    - QA/QC activities
- NBS Molecular Assessment Program (MAP)
  - Site reviews addressing molecular capacities and capabilities in NBS programs
    - 22 NBS program visits since Jan 2011

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NBS information for Physicians, Parents and the Public

- Possible cross-workgroup effort between Lab Standards and Education and Training Workgroups.
  - Address the strengths and limitations of NBS and how to communicate these to the different audiences.
  - Potentially create a tool/product to educate physicians, parents and/or the public on newborn screening.
    - What would this look like?
    - Who would be the target?

NBS information for Physicians, Parents and the Public

- General message – What is screening? What is NBS? How is it different from other screening? What are we trying to find?
- Physicians – Add more information on the limitations of NBS and remind them to act on clinical signs and symptoms regardless of the NBS results.

Questions for the Committee

Any change from the February 2018 recommendation on the APHL Risk Assessment document?

Is there interest in having the Lab Standards and the Education and Training Workgroups jointly pursue creating an educational product on NBS for physicians, parents and/or the public?