Overview of Newborn Screening Laboratory Processes and Quality Management

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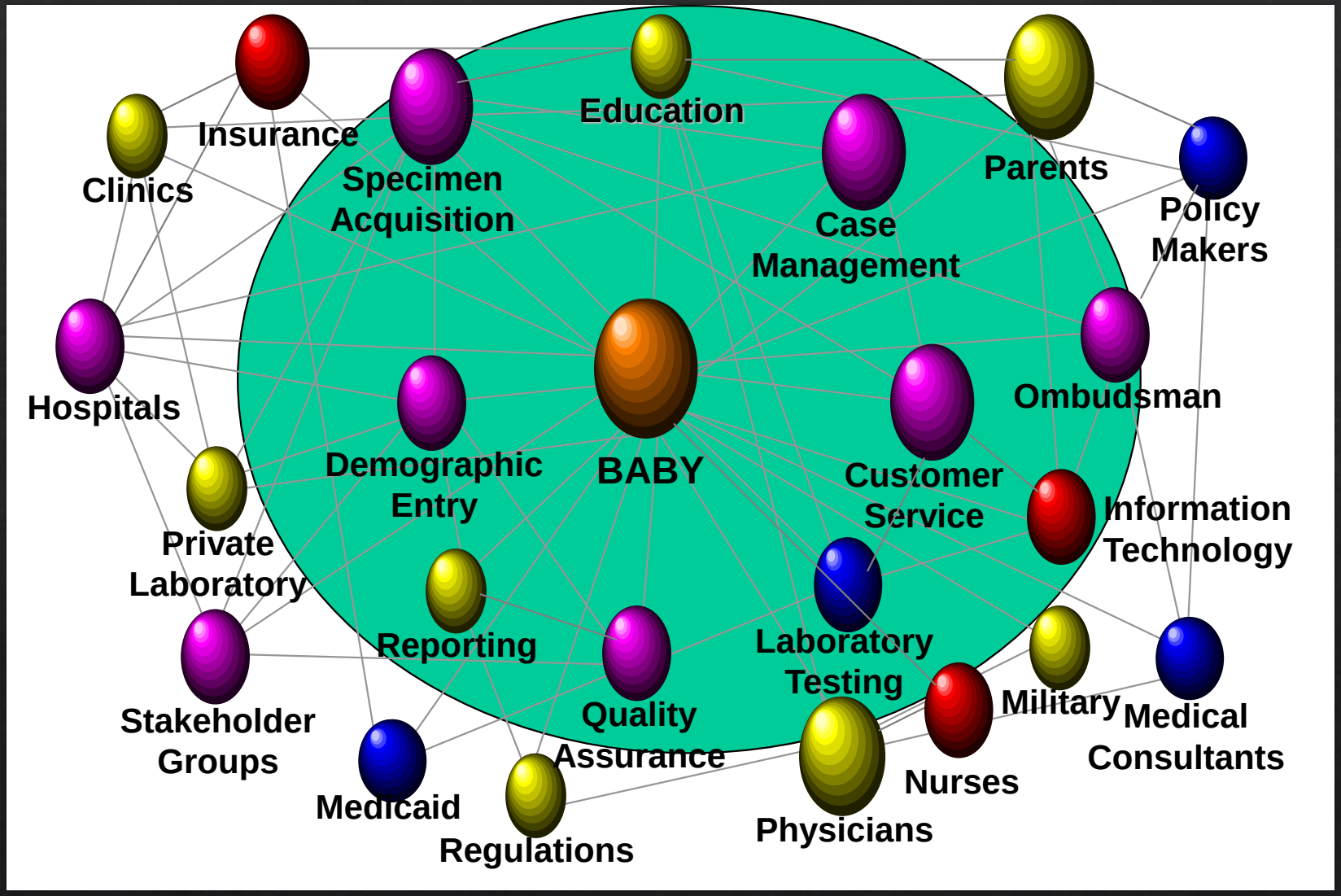
Director, New York State Newborn Screening Program

June 1, 2015

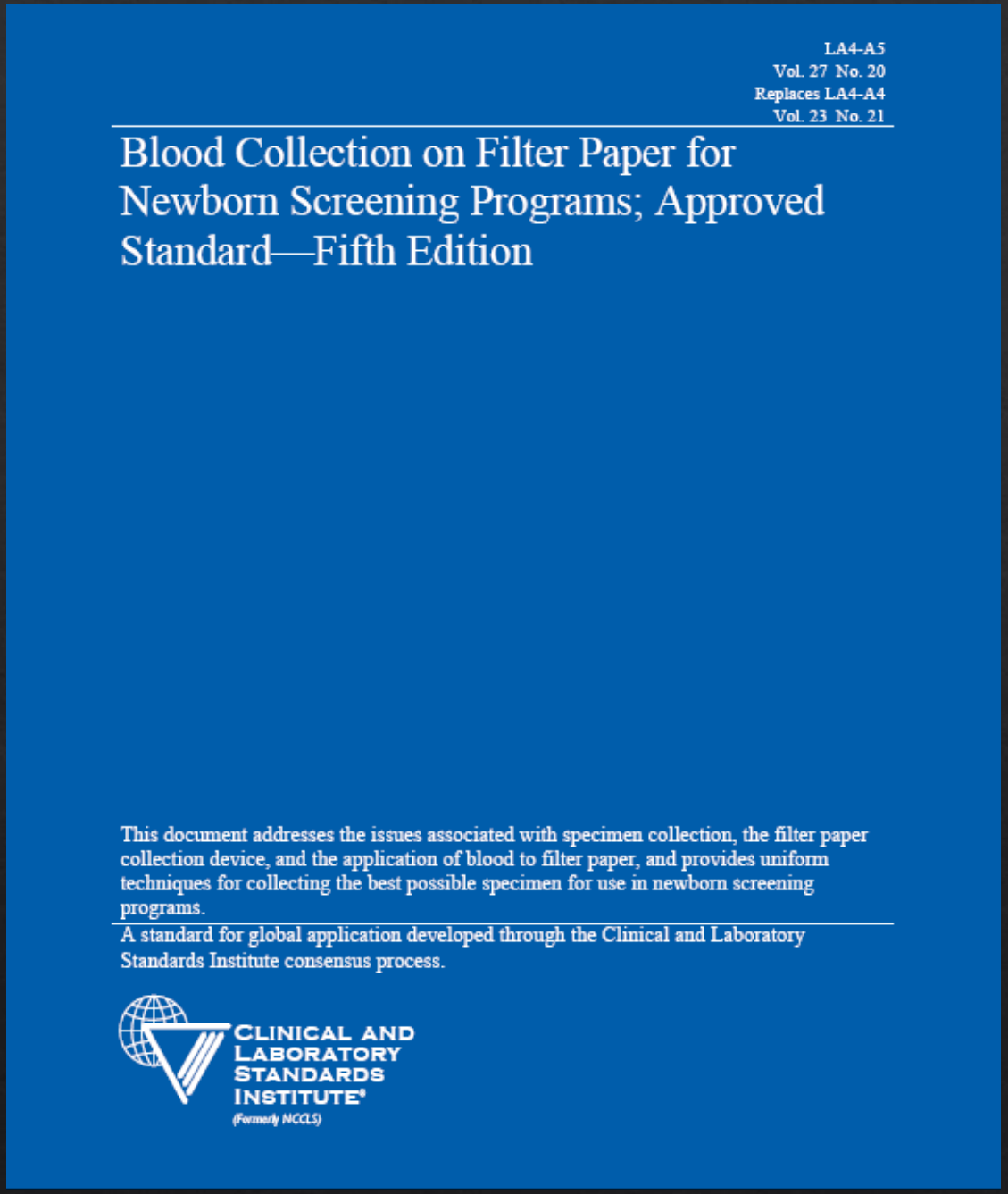
Newborn Screening is a “System”

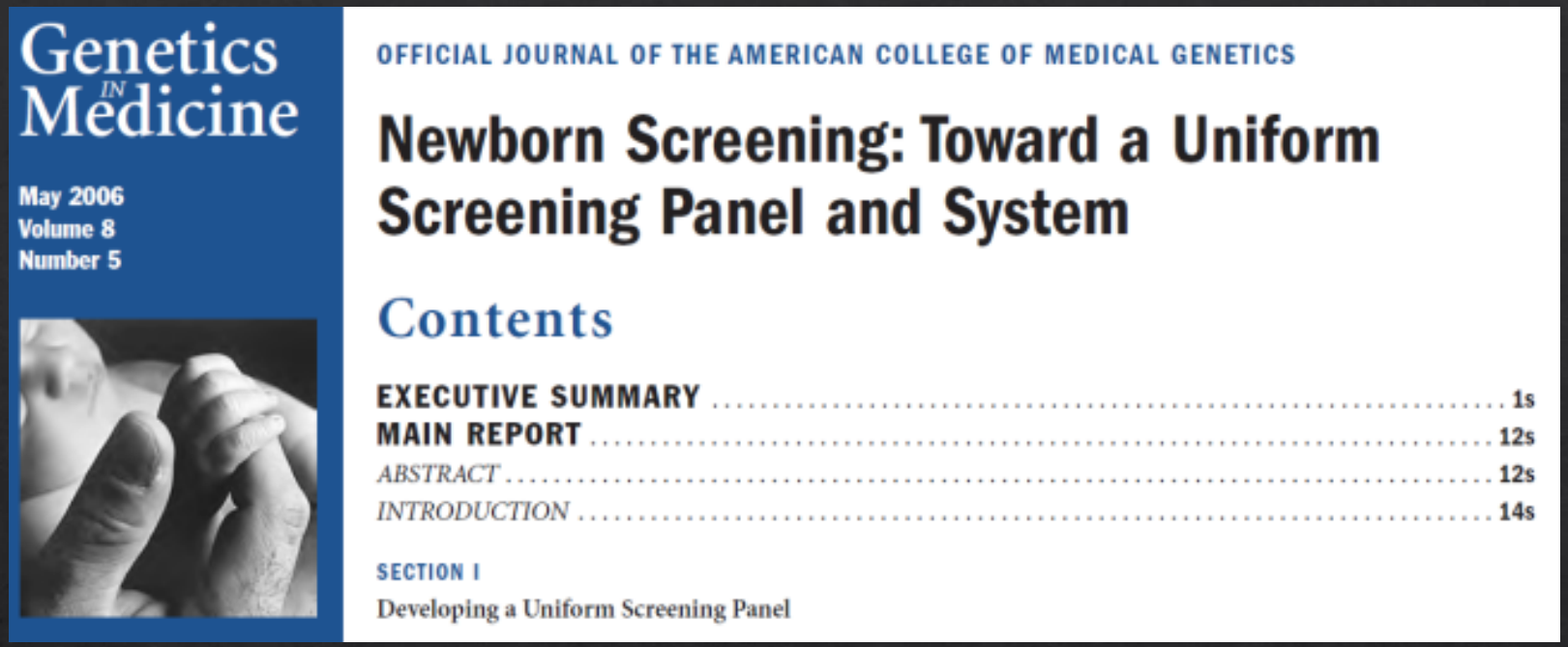


CLSI -Clinical and Laboratory Standards Institute: www.clsi.org

LA04-A5 - Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard - Fifth Edition

LA04-A5-DVD - Making a Difference Through Newborn Screening: Blood Collection on Filter Paper





Genetics IN Medicine

May 2006
Volume 8
Number 5

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF MEDICAL GENETICS

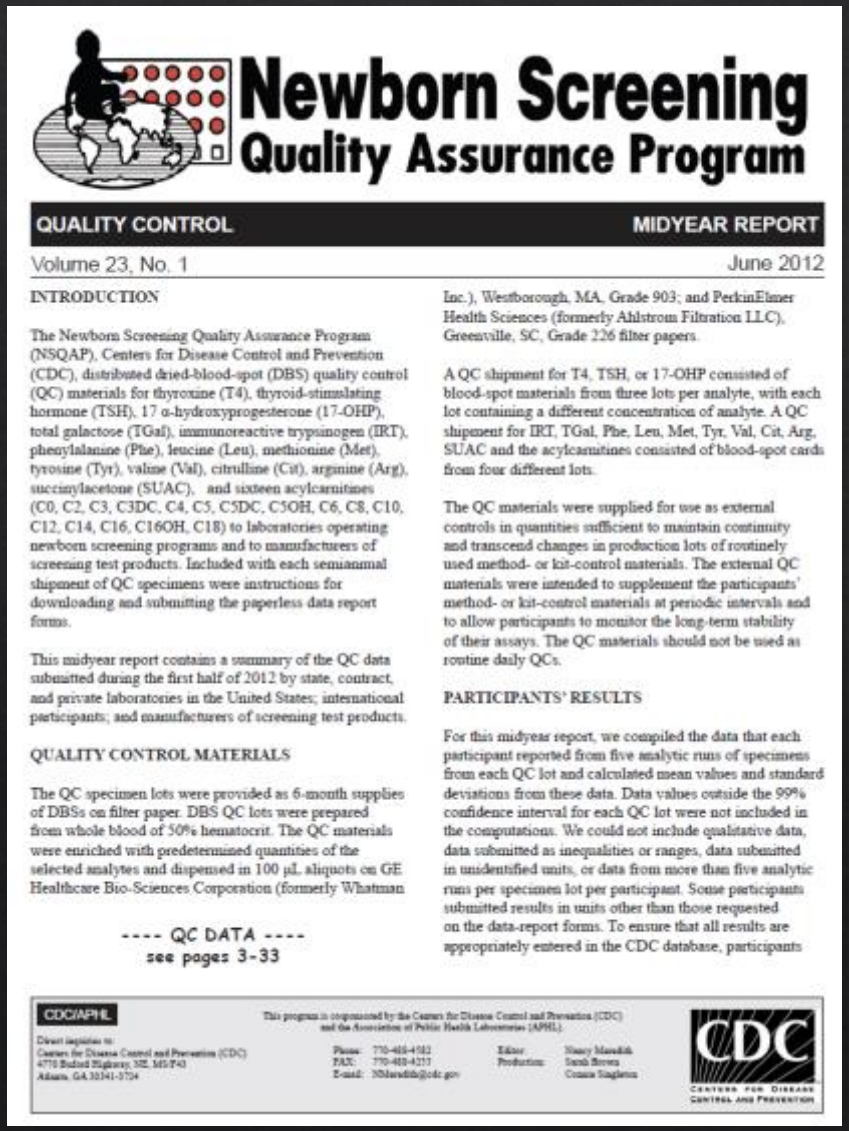
Newborn Screening: Toward a Uniform Screening Panel and System

Contents

Total quality management should be applied to newborn screening programs.

As with any programmatic effort, improvements result from careful and continuous monitoring of key steps in the process, the assessment of that information, and the introduction of changes that continuously improve program performance. Uniform and consistent monitoring of system quality indicators can provide information about the relative performance of screening programs.

Ensuring Quality



Newborn Screening
Quality Assurance Program

QUALITY CONTROL — MIDYEAR REPORT

Volume 23, No. 1 — June 2012

INTRODUCTION

The Newborn Screening Quality Assurance Program (NSQAP), Centers for Disease Control and Prevention (CDC), distributed dried-blood-spot (DBS) quality control (QC) materials for thyroxine (T4), thyroid-stimulating hormone (TSH), 17 α-hydroxyprogesterone (17-OHP), total galactose (TGal), immunoreactive trypsinogen (IRT), phenylalanine (Phe), leucine (Leu), methionine (Met), tyrosine (Tyr), valine (Val), citrulline (Cit), arginine (Arg), succinylacetone (SUAC), and sixteen acylcarnitines (C0, C2, C3, C3DC, C4, C5, C5DC, C5OH, C6, C8, C10, C12, C14, C16, C16OH, C18) to laboratories operating newborn screening programs and to manufacturers of screening test products. Included with each semiannual shipment of QC specimens were instructions for downloading and submitting the paperless data report forms.

This midyear report contains a summary of the QC data submitted during the first half of 2012 by state, contract, and private laboratories in the United States; international participants; and manufacturers of screening test products.

QUALITY CONTROL MATERIALS

The QC specimen lots were provided as 6-month supplies of DBSs on filter paper. DBS QC lots were prepared from whole blood of 50% hematocrit. The QC materials were enriched with predetermined quantities of the selected analytes and dispensed in 100 µL aliquots on GE Healthcare Bio-Sciences Corporation (formerly Whatman Inc.), Westborough, MA, Grade 903; and PerkinElmer Health Sciences (formerly Ahlstrom Filtration LLC), Greenville, SC, Grade 226 filter papers.

A QC shipment for T4, TSH, or 17-OHP consisted of blood-spot materials from three lots per analyte, with each lot containing a different concentration of analyte. A QC shipment for IRT, TGal, Phe, Leu, Met, Tyr, Val, Cit, Arg, SUAC and the acylcarnitines consisted of blood-spot cards from four different lots.

The QC materials were supplied for use as external controls in quantities sufficient to maintain continuity and transcend changes in production lots of routinely used method- or kit-control materials. The external QC materials were intended to supplement the participants' method- or kit-control materials at periodic intervals and to allow participants to monitor the long-term stability of their assays. The QC materials should not be used as routine daily QCs.

PARTICIPANTS' RESULTS

For this midyear report, we compiled the data that each participant reported from five analytic runs of specimens from each QC lot and calculated mean values and standard deviations from these data. Data values outside the 99% confidence interval for each QC lot were not included in the computations. We could not include qualitative data, data submitted as inequalities or ranges, data submitted in unidentified units, or data from more than five analytic runs per specimen lot per participant. Some participants submitted results in units other than those requested on the data-report forms. To ensure that all results are appropriately entered in the CDC database, participants

---- QC DATA ----
see pages 3-33

CDC/APHL

This program is cosponsored by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL).

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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

NewSTEPs

NYSDOH Clinical Laboratory Evaluation Program

Clinical Laboratory Improvement Amendments

COLLEGE OF AMERICAN PATHOLOGISTS

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 61 / No. 2
April 6, 2012

Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening for Inherited Metabolic Disorders

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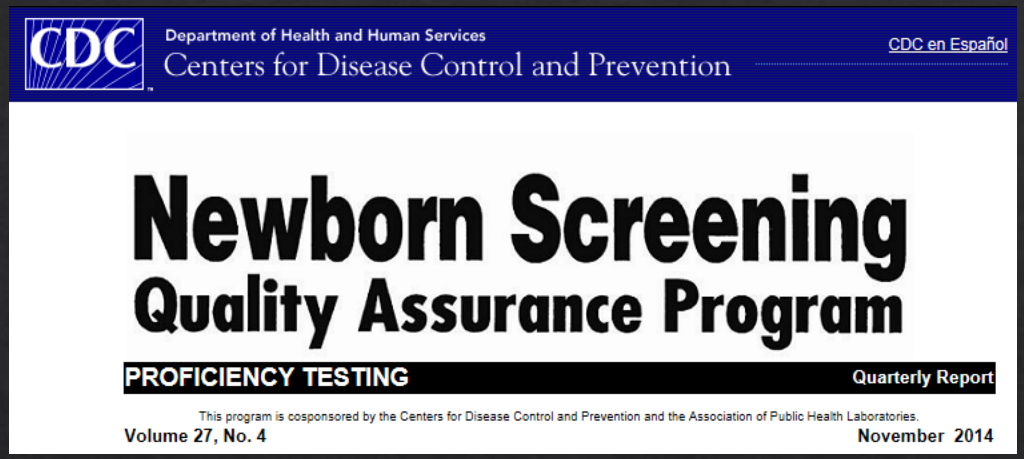
Proficiency Testing

- External
- Specimen exchange
- Internal



Critical Steps Leading to the Implementation of a New Condition

Stage	Description
Initial Development	To show proof of concept, to develop or to evaluate a biological marker, to determine optimal test conditions, test interferences or assess other performance.
Feasibility Assessment	To make modifications an existing (often published) research method to develop a robust, automated method with sufficient performance characteristics that would be appropriate for high-throughput screening in a public health environment. Question addressed is “Can I screen?”
Analytical Validation	Establishment of performance specifications of a new method as per CLIA/CAP requirements. E.g. Accuracy, precision, analytical sensitivity, reportable range, reference intervals
Clinical Performance	To determine whether the test is able to effectively screen for the specific condition. E.g. Clinical sensitivity and specificity; positive and negative predictive values; clinical utility. Question addressed is “Should I screen?”
Implementation	There is evidence that the test has met the threshold requirements from analytical validation and clinical performance studies. State-wide screening can be initiated.
Program Monitoring and Surveillance	To assess all components of the Newborn Screening system and provide information to ensure that program is achieving goals. To identify opportunities for quality improvement.

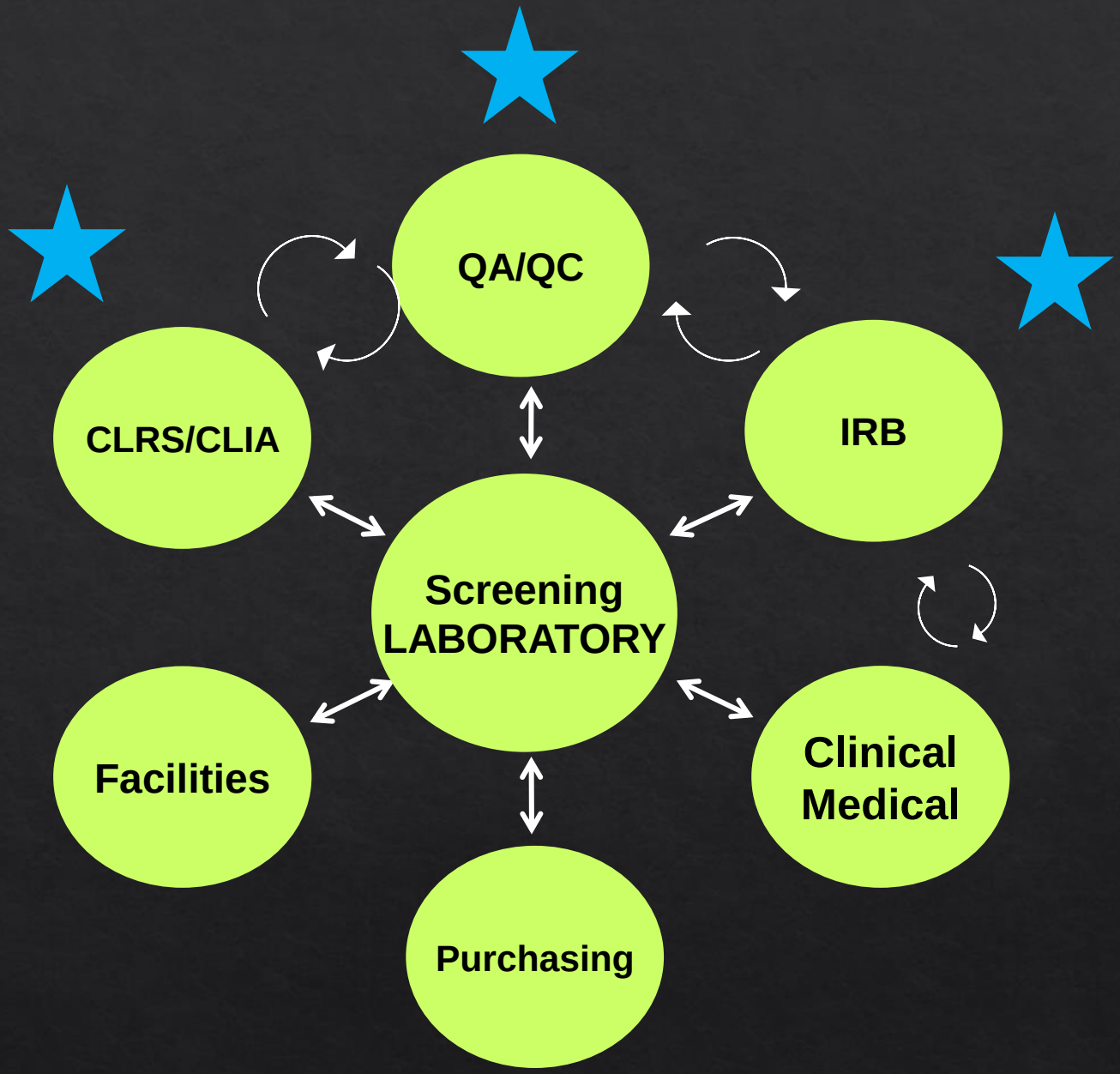
Establishing a New Test

FDA-approved assay – Must establish assay's:

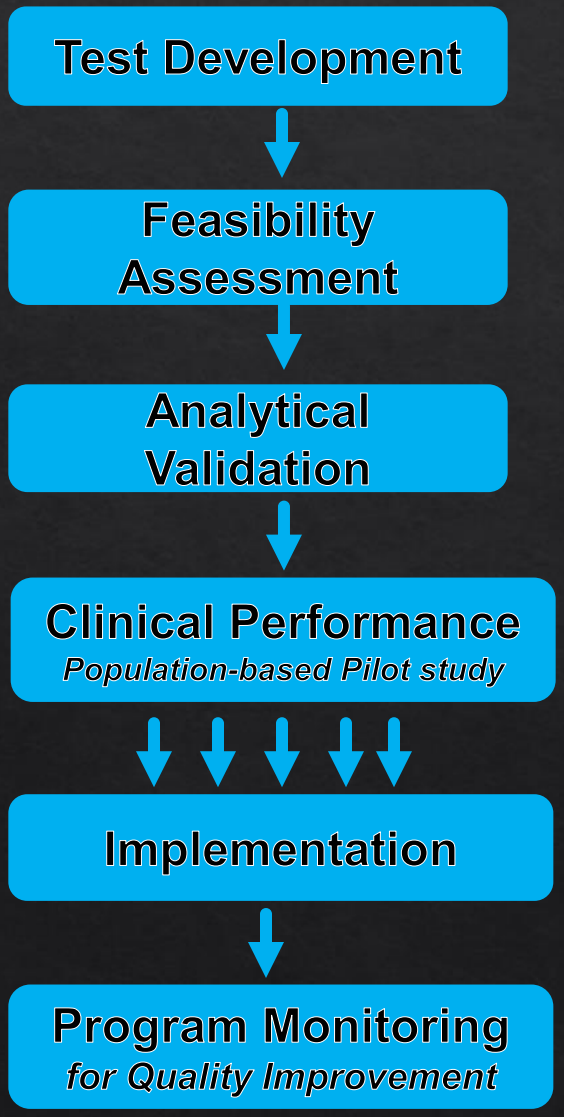
- Accuracy
- Precision
- Reportable range
- Reference intervals

Lab Developed Test – Must establish assay's:

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity
- Reportable range
- Reference intervals
- Other performance characteristics


QA/QC
CLRS/CLIA
IRB
Screening
LABORATORY
Facilities
Clinical
Medical
Purchasing

Systematic Investigation to Determine Whether or Not to Screen for a Condition



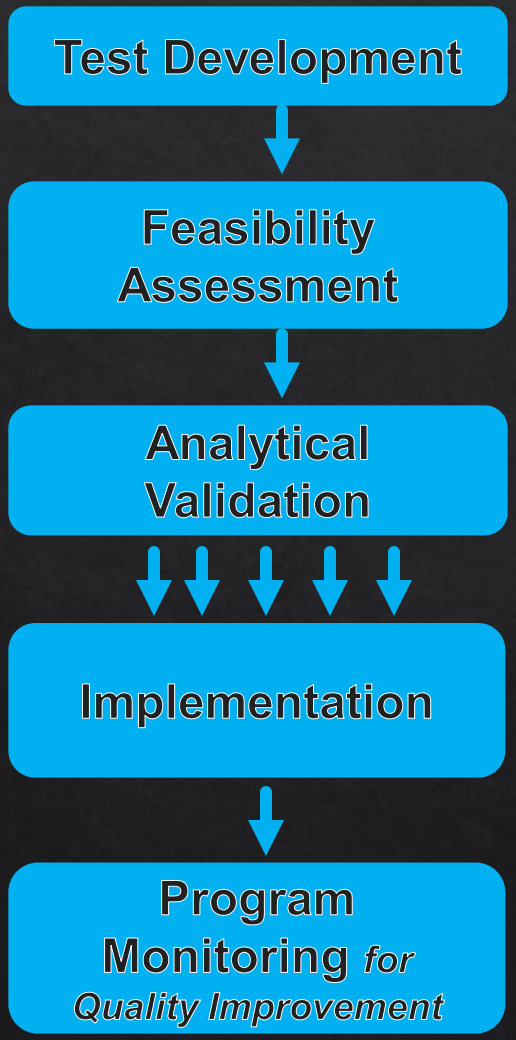
Intent of These Activities:

Collect sufficient evidence to determine whether or not to screen for a certain condition

Note: Program can decide at any point not to continue the process if analytical or clinical performance is not adequate.

This would be an early adopting state engaged in a pilot study … e.g. SCID pilot in WI or MA ~ 2008-9

Implementation of a Screening Test with Well-Documented Clinical Performance



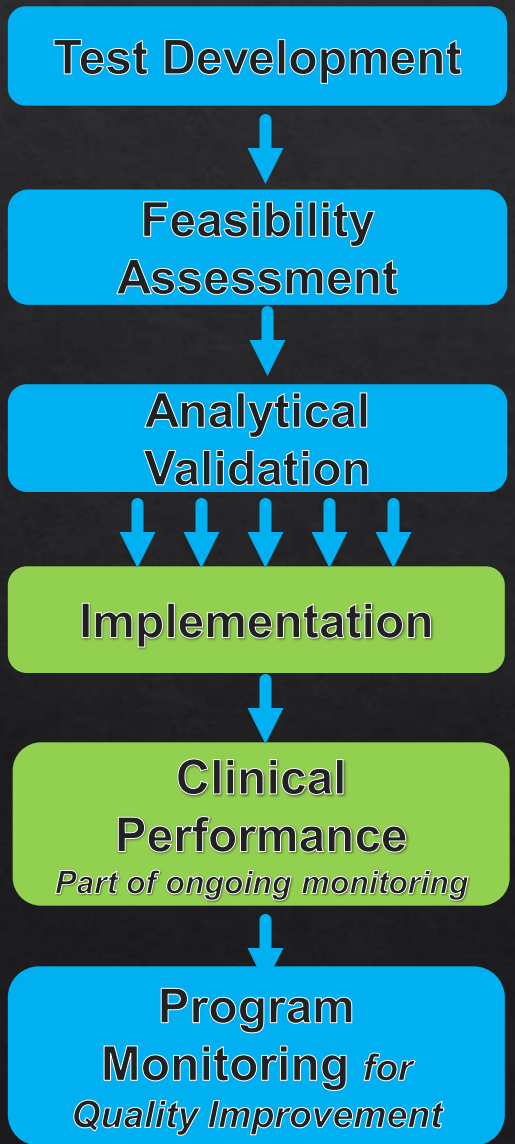
Intent of These Activities

Implement a test that has been shown to have appropriate analytical and clinical performance characteristics.

Note: In this case, pilot studies have already documented the clinical sensitivities/specificities; predictive values and clinical utility of the test.

This is where we currently are with SCID.

Implementation of a Mandated Screening Test Without Well-Documented Clinical Performance



Intent of These Activities

Comply with a time-limited mandate of a legislative authority and implement a test with appropriate analytical performance characteristics.

Note: Program does not have a choice about whether or not to implement screening. Both analytical and clinical performance metrics will be collected after implementation to inform the program about its performance.

Quality Terms

- **Quality Assurance (QA)** – all the planned and systematic activities implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfill requirements for quality. **NOTE**: May be internal or external. Quality assurance is interrelated with quality control.

- **Quality Control (QC)** – the operational techniques and activities that are used to fulfill requirements for quality.

- **Quality Indicators (QI)** - a metric that gives an indication of process or output quality and can be used to make comparisons across different Programs

Analytic Quality

- **Material**
  - Dried blood spots
    - In-house
    - Commercial vendor
      - Kit
      - Non-kit
      - CDC NSQAP
- **Levels**
  - Decision points
    - WNL
    - Abnormal
- **Establishing laboratory range**
  - Replicates ≥ 20 observations
  - Instrument to Instrument
- **Frequency**
  - ≥ 2 control materials per assay
- **Acceptance Criteria**
  - Westgard rules
  - Patients
- **Monitor**
  - Plate to plate
  - Instrument to Instrument
  - Trends
  - Shifts

Laboratories Must Ensure Quality Throughout the System

Pre-analytic

- Test selection and ordering
- Specimen collection, handling, and delivery
- Specimen receipt and accessioning

Analytic

- Specimen preparation
- Test performance
- Monitoring and verification of test accuracy and results
- Documenting test findings

Post-analytic

- Reporting test results
- Turn around time
- Verifying electronic data transfers
- Records and specimen retention

Mom

PLEASE PRINT

Lab I.D. 192718516

Infant's Last Name

Parents,

A blood specimen has been taken from your new baby for testing by the State Newborn Screening Program. This program is described in the brochure "For Your Baby's Health" given to you by hospital staff. To learn the outcome of this important health service, take this note to your baby's doctor, who can obtain the test results at the hospital, or by calling (800) 535-3079. Under NY State law, these results cannot be reported to your doctor and cannot be sent directly to parents.

Do your children have health insurance? If not, they may qualify for NYS's health insurance program, Child Health Plus. Call 1 (800) 522-5006 for information.

Instructions to hospital:
After entering infant's name, remove this pink copy and give it to the parents of this newborn, along with the educational brochure "For Your Baby's Health."

2011-05

SAMPLE

Newborn Screening Program
Serving New York
Since 1965

Wadsworth Center
NYS Department of Health
http://www.wadsworth.org/newborn

PARENT COPY

SUBMITTER COPY
KEEP THIS COPY FOR YOUR RECORDS

1. ACCURATELY FILL OUT INFORMATION ON FORM
2. TEAR OUT & KEEP GREEN COPY AS YOUR PROOF OF SPECIMEN COLLECTION
3. COLLECT BLOOD

(SEE REVERSE OF FORM FOR BLOOD COLLECTION INSTRUCTIONS)

Hospital

NEWBORN SCREENING BLOOD COLLECTION FORM
DO NOT USE AFTER JULY 2013

DOH USE ONLY

PRINT CLEARLY

DO NOT WRITE IN OR COVER SHADED AREA

Initial Specimen ☐ Repeat Specimen ☐ Male ☐ Female

Single Birth ☐ Twin A ☐ or B ☐ Other ☐

Infant's Last Name:

Infant's First Name:

AKA:

Infant's Ethnicity/R
White ☐ Asi
Black ☐ Oth
Hisp. ☐ Nat Am

NICU ☐

Date of Birth: MM DD YYYY

Time of Birth: (Military Time)

Gestational Age: (Weeks/Days)

Mother's A

Date of Specimen: MM DD YYYY

Time of Collection: (Military Time)

Birth Weight: (Grams Only)

Infant's Medical Record No.:

Infant's Age When Specimen Collected:
Less Than 24 hours ☐
More Than 24 hours ☐

Transfused ☐ Date
TPN ☐
Antibiotics ☐

Mother's Name and Address:
Last First
Addres Apt.#
Zip:
Tel. ( )

Lab

Maternal HBsAg Test Re
Pos. ☐ Neg. ☐ U
HIV Testing
Prior Maternal | In-Hos
A B C D | E F

Hospital Name & Address:
City:

Hospital of Birth?
Yes ☐ No ☐ Homebi
Adoption ☐
Foster C

Hospital PFI Code:

Infant's Primary Care Physician:
Name:
Address:
Zip:
Tel. ( )

Physician's License No.:

Previous Lab ID#:

Completed By:

Specimen Drawn By:

Notes:

Lab I.D. 318227711

NBS LAB COPY SN

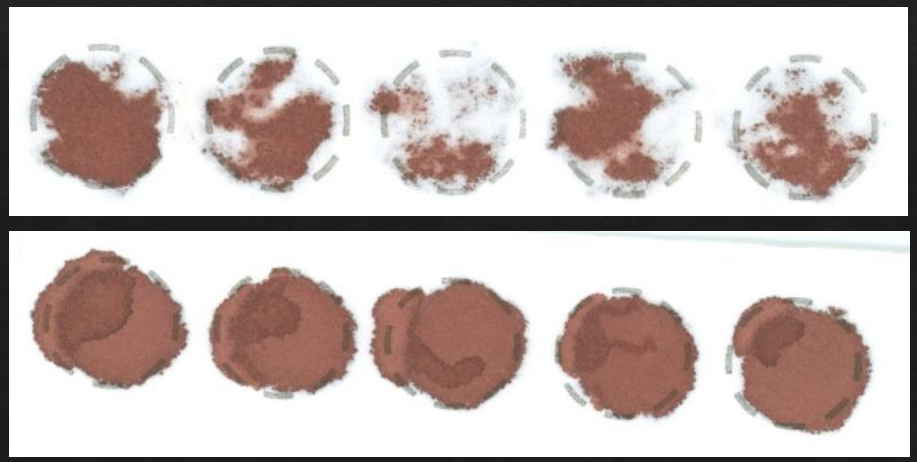
SEE REVERSE SIDE FOR INSTRUCTIONS

SN Lab I.D. 318227711

SATURATE ALL CIRCLES COMPLETELY

Pre-Analytic Quality

- Time from collection to receipt
- Notification to hospital after receipt
- Time from receipt to accessioning



Newborn Screening Report Card

2015 Quarter 1, specimens received 1/1/2015 – 3/31/2015

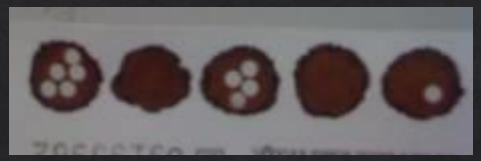
Newborn screening coordinator: , Nurse Manager
CEO: , Chief Executive Officer
Nursery manager: Nurse Manager
NICU manager: ,
QA contact: Nurse Manager

This report contains information regarding your hospital's performance in timely submission of appropriately collected newborn screening specimens to the state lab in Albany for quarter 1, 2015 (1/1/2015 - 3/31/2015). The report outlines your facility's performance for unsuitable specimens and specimen turnaround time, and is being sent to your hospital CEO, Newborn Screening Coordinator, Nurse Managers of the Nursery and NICU and the NBS Quality Assurance Cont

Proper specimen collection and timely submission saves lives!

Turnaround Time (TAT) Report: Turnaround time is the amount of time it takes for a specimen to reach the newborn screening lab after collection. TAT is calculated as the number of days between specimen collection and specimen rece

New York State Public Health Law, Section 2500-a, Subpart 69-1.3 g specifies that all specimens shall be forwarded to testing laboratory within twenty-four (24) hours of collection using the testing laboratory's delivery service or an equivalent arrangement designed to ensure delivery of specimens to the testing laboratory within no later than forty-e (48) hours after collection.



Analytic

Galactosemia – fluorometric assay
Biotinidase Deficiency – colorimetric assay

Amino Acids
Fatty Acid Oxidation
Organic Acids
Krabbe
ALD

Hemoglobinopathies

Cystic Fibrosis
- IRT

Congenital Adrenal Hyperplasia
- 17OHP

Congenital Hypothyroidism
- T4
- TSH

Severe Combined Immunodeficiency

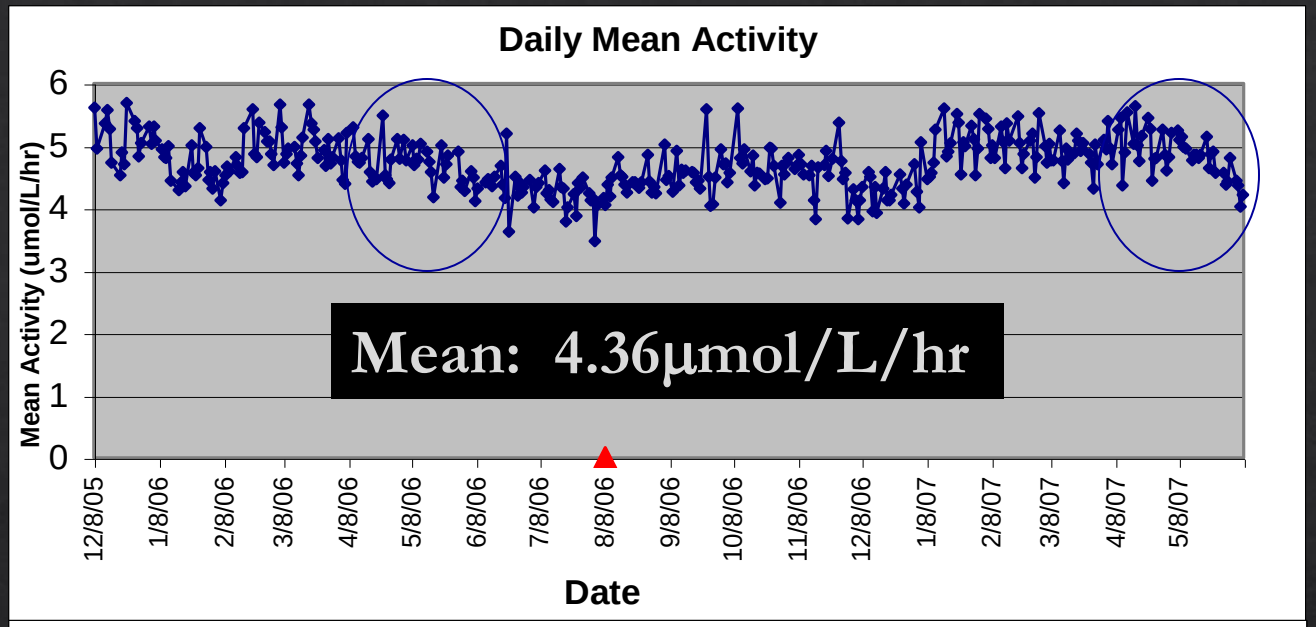
Quality Control Data: Daily Mean Activity

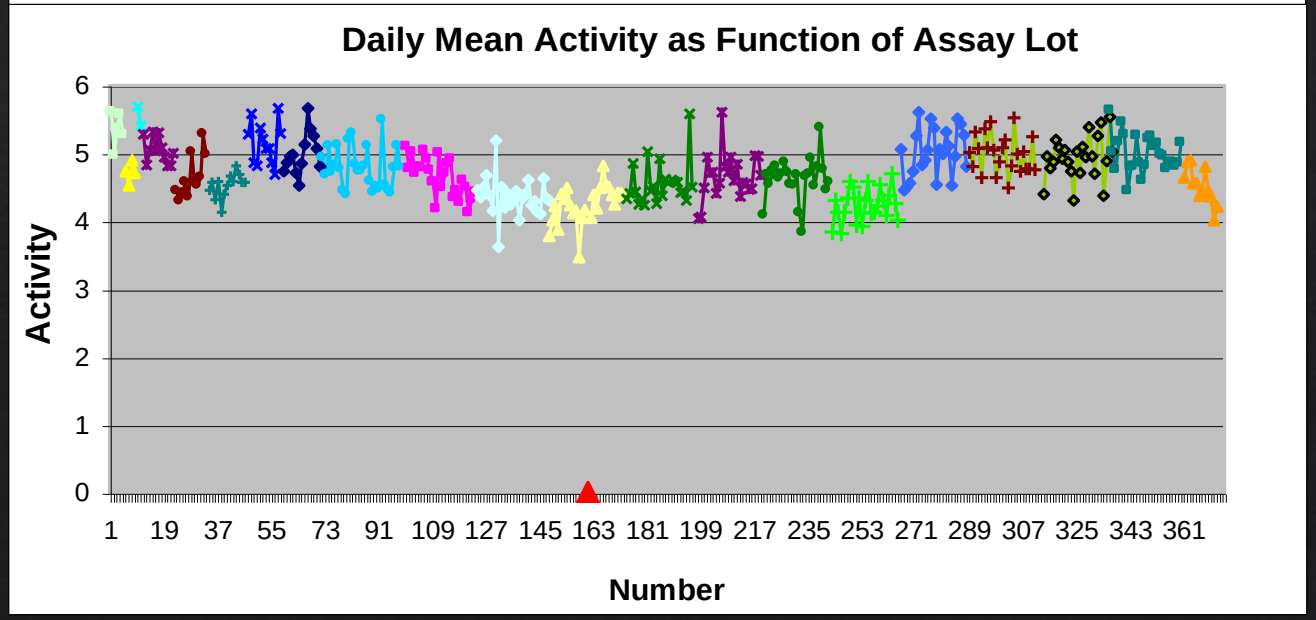
▲ Live Screening

N=156,816

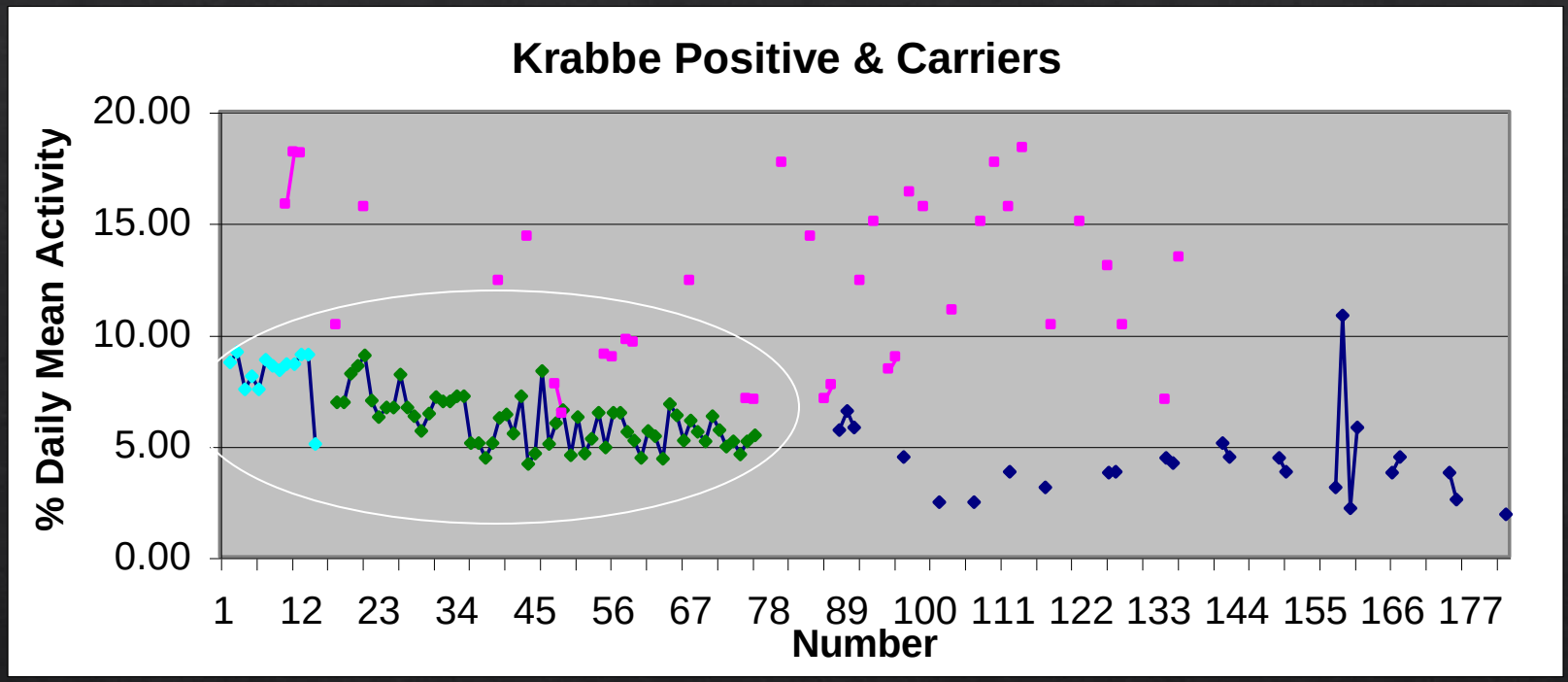
Expected Actionable Results:
N = 54 began at <10%
N = 142 at <12%

n = 19 < 8%
n = 35 ≤ 10%
n = 88 ≤ 12%





Krabbe Controls



Pink: Obligate carriers

Dark Blue: Krabbe controls, from older patients

Light blue: Specimen from cord blood

Green: Same newborn as cord blood, seven days old

Mean: 5.15% of the daily mean, 0.225mmol/L/hr

SCID Cutoff Adjustment

Example from NJ NBS

>37 weeks	BORD	PRE	Total Abnormal
June 30, 2014 to Oct 7, 2014 26,835 specimens	89 (0.33%)	14 (0.05%)	103 (0.38%)
Oct 8, 2014 to Jan 31, 2015 32,082 specimens	13 (0.04%)	3 (0.009%)	16 (0.05%)

Why Do We Need Residual DBS?

- Frequency of condition (SCID ~1 in 50,000)
- Quality control material – matrix considerations
- Operational considerations
- Unsuitability of samples from transplanted patients
- Population based variation not detected in small scale studies; populations within populations
- Governance by Institutional Review Boards

Frequency of Condition

Need to Find a Positive!

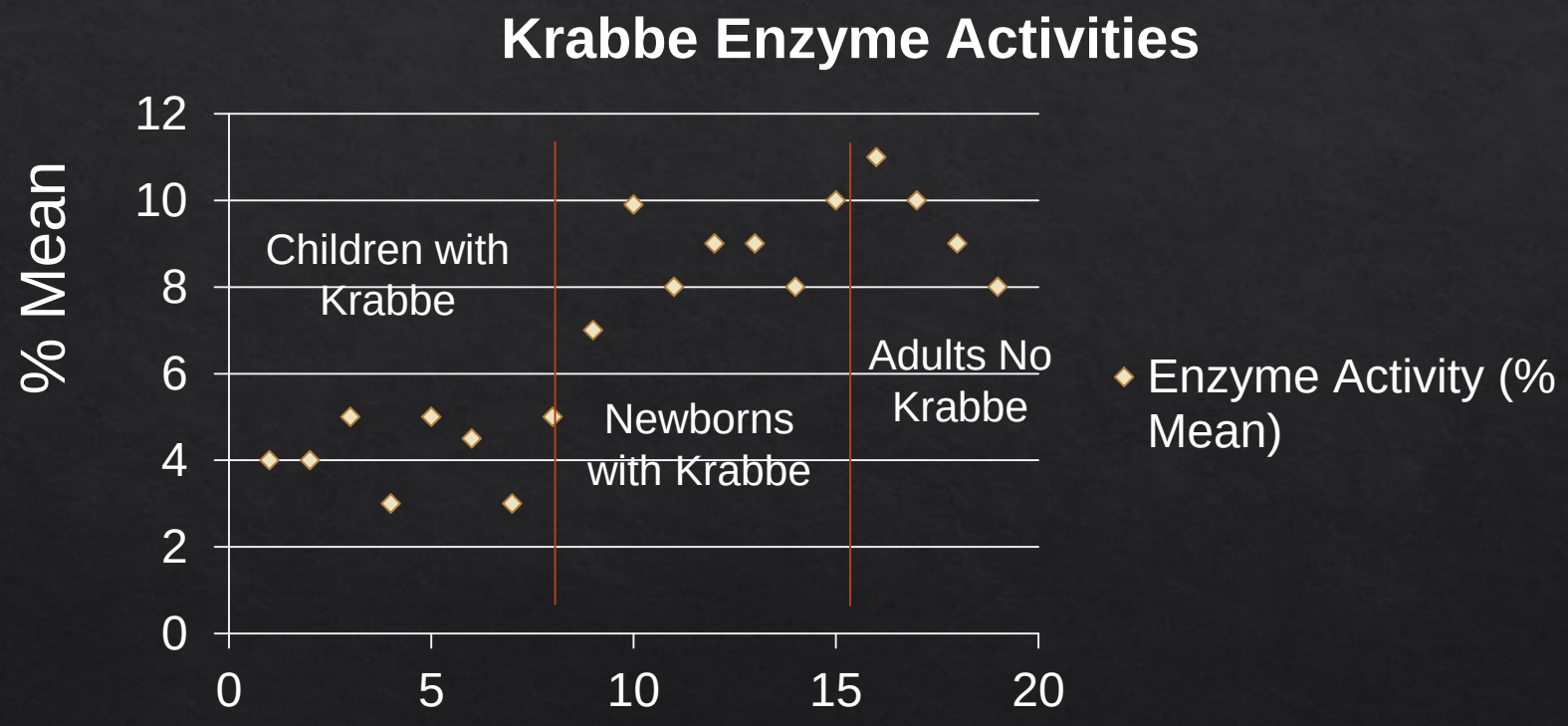
Why Do We Need Newborn DBS??

Validation – Quality control material – matrix considerations

- Hematocrit (volume of RBCs) varies; NBS based on 'average'
- White blood cell count is higher in babies
- Need to use the same matrix as the test matrix; i.e. DBS from capillaries, not liquid blood in anticoagulants; FDA requirement – off label use
- Need to have positive controls to ensure the test works
- Need to avoid increased family anxiety – calling carriers as positive; need to study carriers also

Why Do We Need Newborn DBS??

Example of patient / matrix difference



Premature Infants?

Transfused Infants?

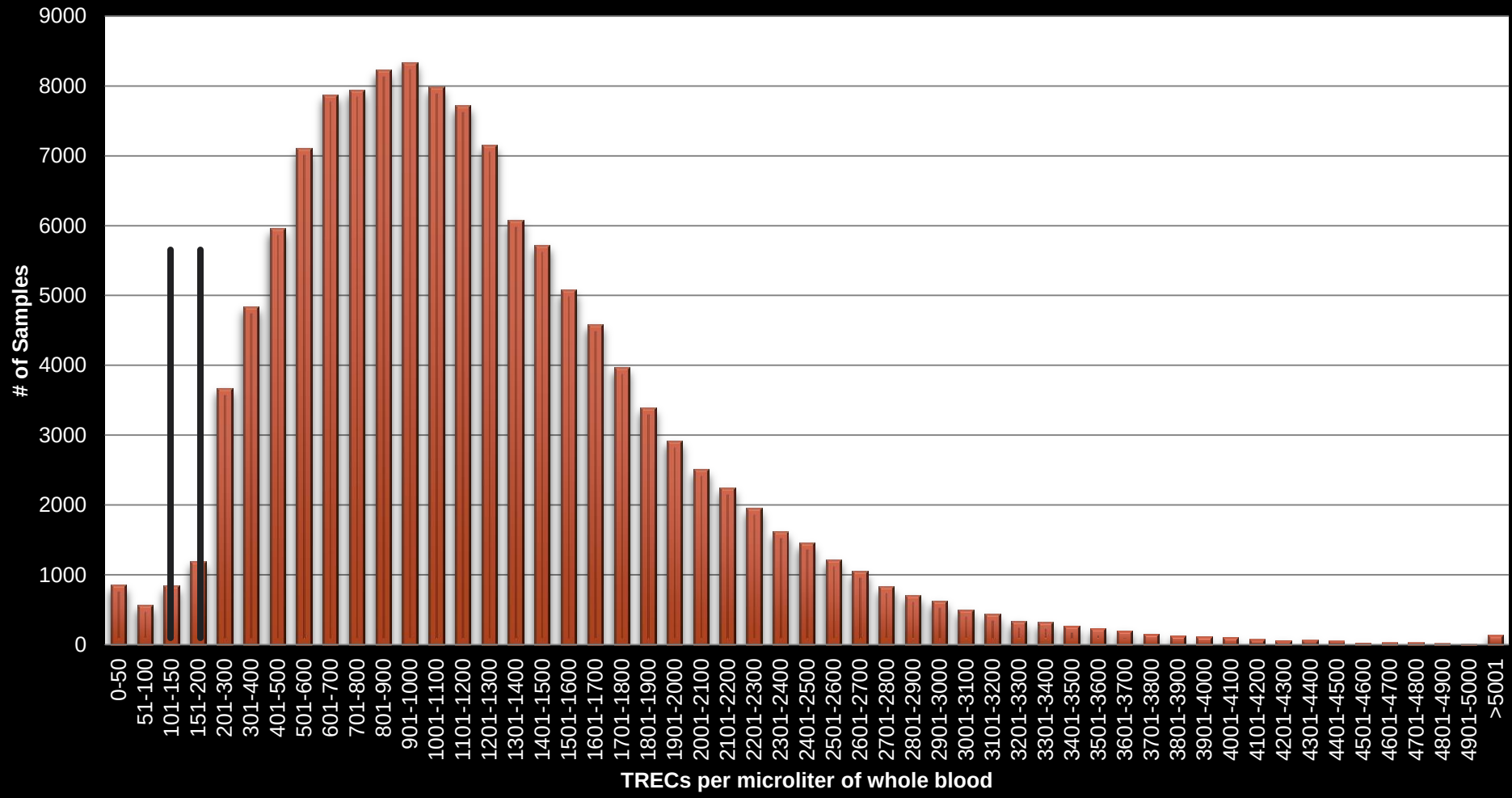
Why Do We Need Newborn DBS??

Child's Immune System Replaced By Donor

(can't use blood sample)

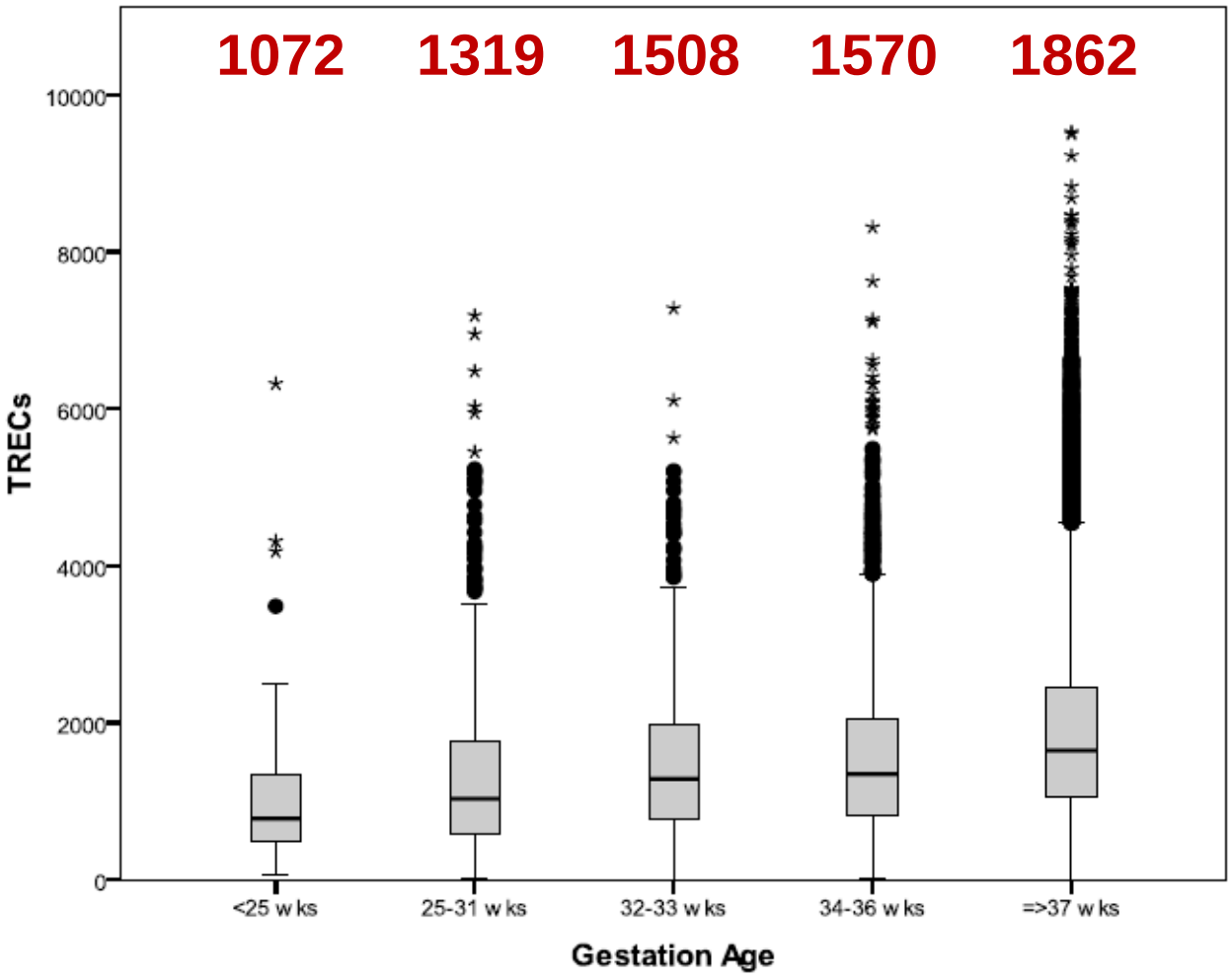
Population Based Variability

Need to Assay Many Samples



Why Do We Need Newborn DBS??

Premature infants have an immature thymus, but premature babies can still have SCID !



Adults have low TRECs. All would be screen positive!!

Why Do We Need Newborn DBS??

Institutional Review Boards

- Expedited, but need to get consent to pull 'by name', thus need to write a new protocol and consent form for any new condition
- Need to work through physicians to identify patients in their practices; reliance on the messenger
- Need to limit to patients born in years specimens are saved and for those babies you can find
- Need to book keep for samples, consents etc.
- In New York, need review of protocol execution after IRB approval; occurs when consent is received, but prior to pulling sample from the repository

Routine validation samples need IRB also; de-identified

Special Thanks to Dr. Scott Shone – NJ NBS for some slides