



# STRATEGIES TO IMPROVE THE SPECIFICITY OF NBS RESULTS

CLIR: A USER'S PERSPECTIVE

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XII SLEIMPN 2022  
May 5, 2022

I have no conflicts of interest related  
to this material.

# INTRODUCTORY POINTS & DEFINITIONS

- Collaborative Laboratory Integrated Reports (CLIR – [clir.mayo.edu](http://clir.mayo.edu))
- Specificity improvements – reduce false positive results without sacrificing true positives
- False positive results – any result identified by the lab that results in notification to the family of an unaffected child

# SPECIFICITY IN NEWBORN SCREENING (NBS)

## WHY DOES IT MATTER?

- An ideal screening assay should be highly sensitive and highly specific
  - Identify the individuals at increased risk for the screening target and minimize disruption to those not at risk
- False positive (FP) results are not benign for families, particularly in newborns
  - Stress, fear, \$\$\$, doubt
- From the NBS system perspective – FP results have a cost
  - Additional repeats, additional team members, testing, short and long term follow-up

# CLIR

## POST-ANALYTICAL TOOLS SUITE

What is it and how can it help?

The screenshot shows the CLIR Post-Analytical Tools Suite interface. At the top left is the Mayo Clinic logo. The top right features the CLIR logo and the user email Hall.Patricia@mayo.edu. The main navigation bar includes: Home, Resources, Location Data, Post-Analytical Tools, Productivity Tools, Tasks, Admin, My Account, and Sign Out. The 'Application' dropdown is set to 'NBS ALL'. The interface is divided into two main sections. The left section contains two panels: 'Post-Analytical Tools' with links for Single Condition Tools, All Conditions Tool, Tool Runner, Dual Scatter Plots, and Dual Scatter Plot Runner; and 'Data Uploads' with links for Reference Data Uploads and Case Data Uploads. The right section is titled 'Dates of Last Data Submissions' and includes filter tabs for 'All', 'Submitted', and 'Missing'. Below the filters is a table with columns for Location, Reference, Cutoffs, Cases, and Metrics. The 'Location' column lists: Africa, Asia, Australia, Europe, Middle East, North America, South America, USA, and Utilities.

MAYO CLINIC

Application: NBS ALL

CLIR  
Hall.Patricia@mayo.edu

Home Resources Location Data Post-Analytical Tools Productivity Tools Tasks Admin My Account Sign Out

### Post-Analytical Tools

- Single Condition Tools
- All Conditions Tool
- Tool Runner
- Dual Scatter Plots
- Dual Scatter Plot Runner

### Data Uploads

- Reference Data Uploads
- Case Data Uploads

### Dates of Last Data Submissions

All Submitted Missing

Location	Reference	Cutoffs	Cases	Metrics
▶ Africa				
▶ Asia				
▶ Australia				
▶ Europe				
▶ Middle East				
▶ North America				
▶ South America				
▶ USA				
▶ Utilities				

# WHAT IS CLIR?

## HOW CAN IT HELP NBS?

### History

- Region 4 Stork (R4S) originated as a group of tools for performance improvement in NBS, backed by HRSA
- Collected cases and reference percentiles from laboratories around the world
- Important first step for establishing collaboration and demonstrating data equivalence

### Current state

- CLIR is a Mayo Clinic backed endeavor
- Collects full profiles of cases, controls and false positives
- Adjustment of submitted data for covariates and location – continuous rather than discrete reference range bins
- Submission of data required for participation

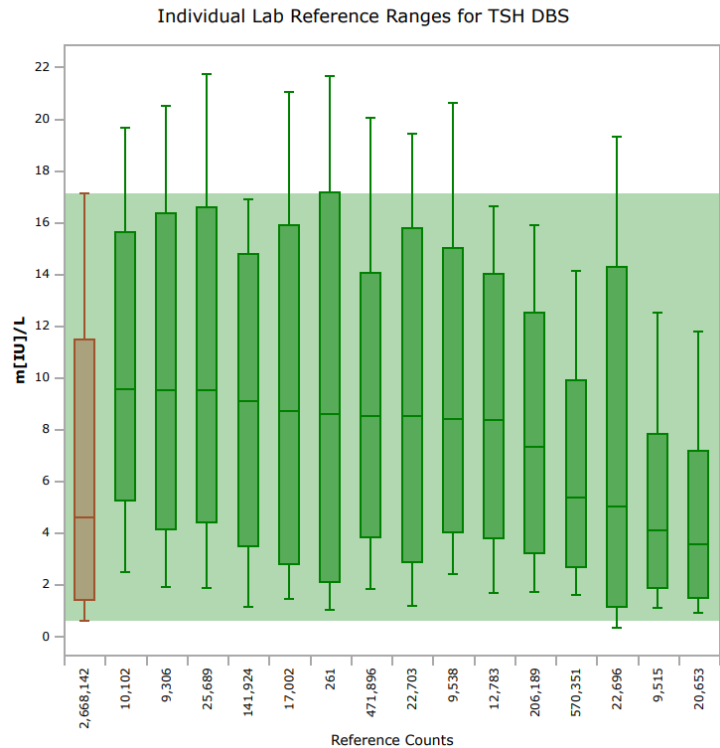
# IMPROVING SPECIFICITY WITH CLIR

- Multifaceted approach, none of it is passive
  - Data evaluation
    - Provides visual examination of your data against those of other labs
    - Spot check of analytical performance (do you have a fussy analyte?)
  - Algorithm refinement & marker identification
    - Potential to evolve from single marker to multiple (PHE + PHE/TYR)
  - Evaluation of case results using post-analytical tools
    - Offline process
  - Evaluation of screening results
    - Inline process
- Philosophy Shift: An abnormal result is not simply a deviation from “normal”, it must resemble known disease profiles.

# DATA EVALUATION

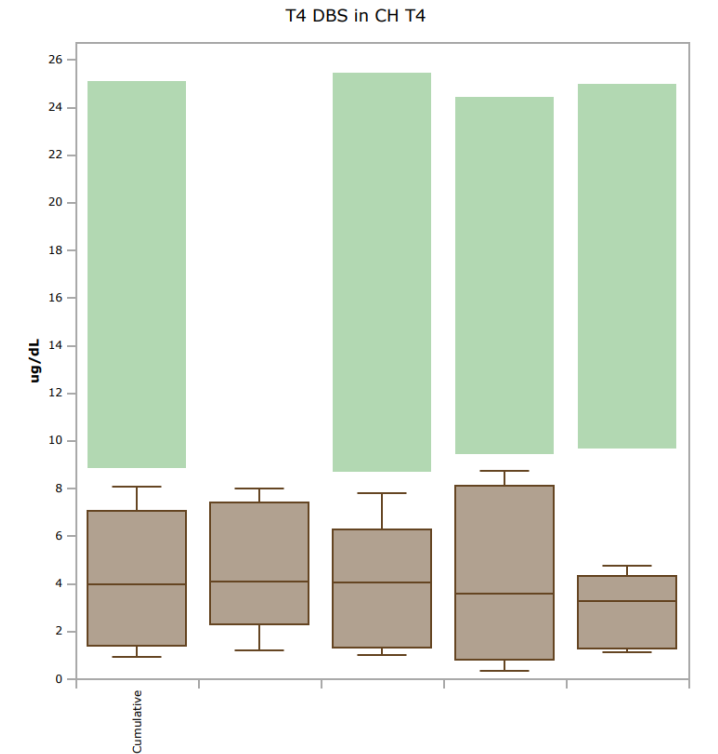
- Reference range comparison
- Disease range comparison

Reference Range Comparison Application: NBS ALL



- Once data have been submitted, can compare (anonymously) to peer labs
- Available for reference data and targeted conditions

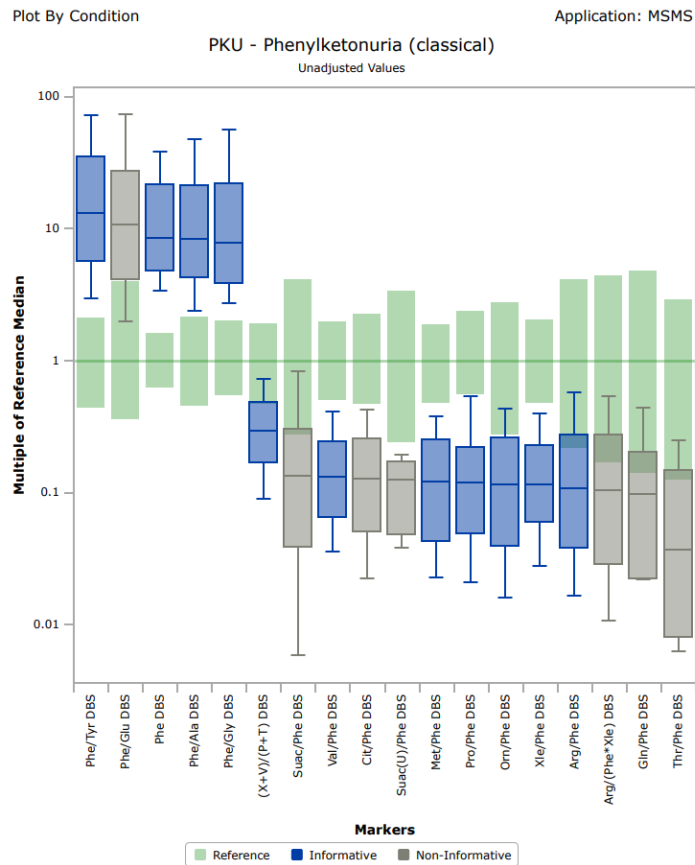
Disease Range Comparison Application: NBS ALL



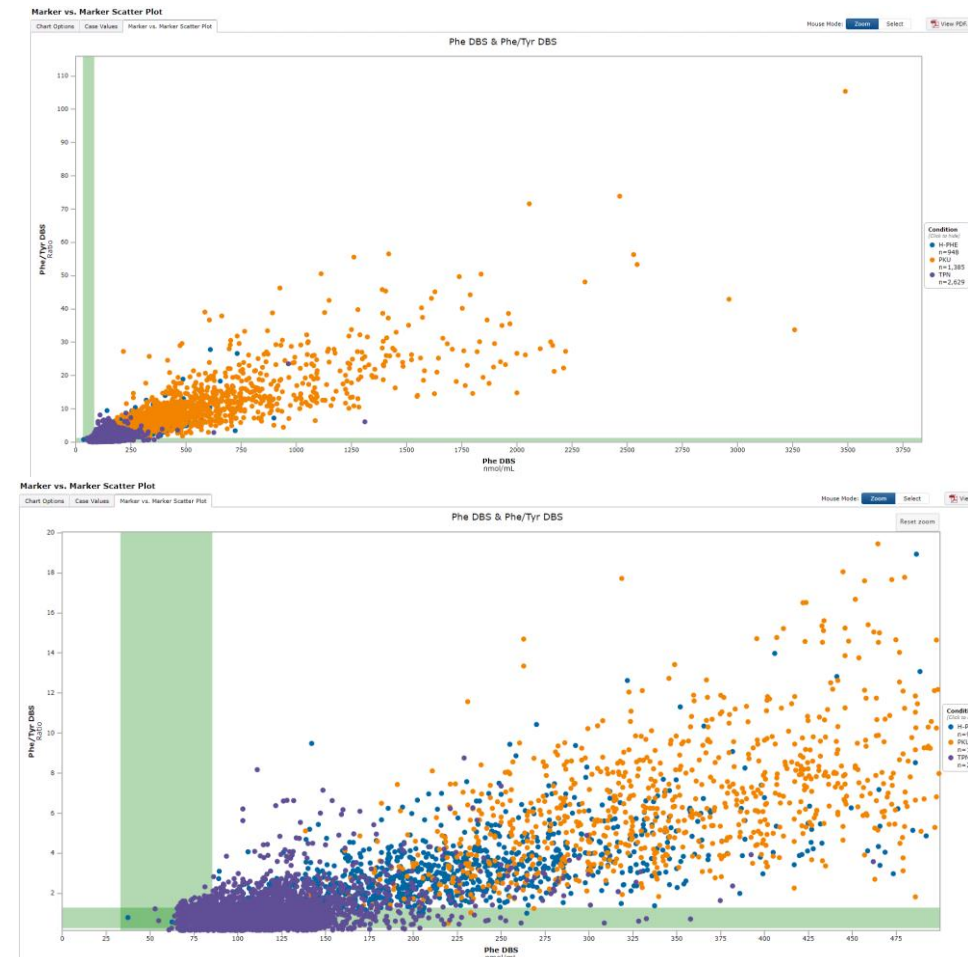


# ALGORITHM REFINEMENT

- Plot by Condition
- Marker vs Marker Plot



- Ability to leverage cumulative data for rare conditions
- Case counts:
  - PKU: 1546
  - MCAD: 1996
  - VLCAD: 448
  - MSUD: 297



# EVALUATION OF CASE LEVEL RESULTS

- Single condition tools
- Dual scatter plots

## Single Condition Tool: Pompe

Run Single | Score Calculation

North America/USA/MAYO/RST (Rochester)

Upload... | Download CSV Template | Clear

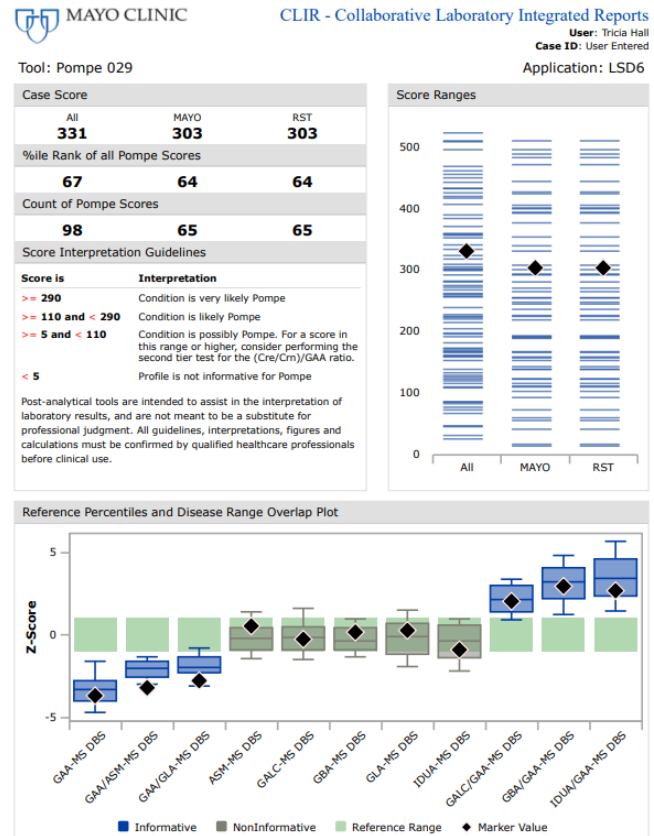
Marker / Covariate	Value	Unit
<b>Covariates</b>		
BW	3200	>=250 and <=10000
Age hr	24	>0 and <=10000
<b>Informative Low Markers</b>		
GAA-MS DBS	1.21	nmol/mL/hr
<b>Differentiator Markers</b>		
ASM-MS DBS	9.54	nmol/mL/hr
GALC-MS DBS	5.26	nmol/mL/hr
GBA-MS DBS	17.45	nmol/mL/hr
GLA-MS DBS	19.23	nmol/mL/hr
IDUA-MS DBS	5.49	nmol/mL/hr

Aggregator: Mayo Clinic [MAYO]

Reference Values: Cumulative

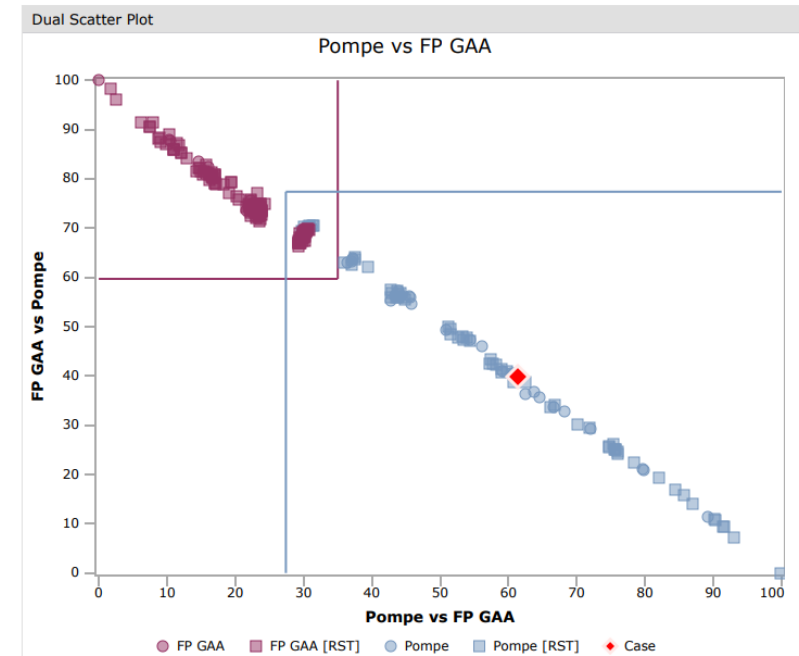
Date Limit: None | 4/29/2022

View PDF... | Submit | Reset | Calculate



## Tool: Pompe vs FP GAA 025

Application: LSD6



# INTEGRATION INTO LABORATORY WORKFLOW

- Tool runner
- Dual scatter plot runner

**Tool Runner**

Tool Runner | Batch Summary | Informatives (0) | Non-Informatives (2) | Exceptions Triggered (2) | Case Summary

Reference Values  
 Cumulative  Site  Include Cumulative/Site Score Comparison

Upload Multiple Case File Download CSV Template

Select... Done

KMPX\_3897972.csv  
File(s) uploaded successfully.

Results to CSV File Run Selected Tools

Tool Runner Results Summary

Cases: 70 Tools Run: 210  
Batch ID: Batch ID 3897972 Code KMPX

North America/USA/MAYO/RST (Rochester)

Location User Default

Released

- Site Specific Tools
- Shared Tools
  - Krabbe
  - Pompe
  - Gaucher
  - Fabry
  - NPAB
  - MPS I

- High throughput analysis
- Can analyze a “run” (plate) for all targeted condition(s) simultaneously
- Customizable for screening panel variations

**Dual Scatter Plot Runner: MPS I vs FP IDUA**

Dual Scatter Runner | Results | Results Flow | Results Pie

North America/USA/MAYO/RST (Rochester)

Reference Range Values  
Cumulative Mayo Clinic [MAYO]

Filter Cases  
Scores:  Informative  Non-Zero Guidelines:  Tool  Default %iles

- MPS I must be an Informative Score
- FP IDUA must be an Informative Score
- Both MPS I and FP IDUA must be Informative Scores
- Either MPS I or FP IDUA must be an Informative Score
- Do Not Filter Cases

MPS I  
FP IDUA

Zoom Indeterminate Cases  
 Perform Zoom (if applicable)

Upload Multiple Case File Download CSV Template

Select... Done

KMPX\_3897972.csv  
File(s) uploaded successfully.

Results to CSV file Run Dual Scatter Plot All Results

Dual Scatter Plot Runner Results Summary

Case Count: 70  
Scatter Run: 70 Scatter Missing Data: 0

File Name: KMPX\_3897972.csv  
Batch ID: Batch ID 3897972 Code KMPX

[See Results Tab for Successfully Run Cases](#)

- Useful for confirmation runs
- Multiple repeats for same condition with a known FP profile type

# IMPROVING SPECIFICITY OF NBS

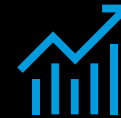
## NOT A ONE-TIME ACTIVITY

- Quality improvement can be (?should be / must be?) iterative
- CLIR offers many ways for laboratories and screening programs to reduce FP screens
- Does not all need to be done at once



### Adjust existing cutoffs

Can reduce FP when a gap exists between reference and disease range



### Dual scatter for common FP

What are your common FP – is there a pattern? Reduce high yield conditions



### Full integration

CLIR fully integrated into algorithm and reporting

## ACKNOWLEDGEMENTS

- Mayo Clinic Biochemical Genetics Laboratory
- Georgia Department of Public Health NBS Laboratory
- Organizing Committee

# QUESTIONS & ANSWERS

