MAYO CLINIC

STRATEGIES TO IMPROVE THE SPECIFICITY OF NBS RESULTS

CLIR: A USER'S PERSPECTIVE

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Congreso Latinoamericano de Errores Innatos del Metabolismo Y Pesquisa Neonatal
EN LA ERA DE LAS ÓMICAS

I have no conflicts of interest related to this material.

INTRODUCTORY POINTS & DEFINITIONS

- Collaborative Laboratory Integrated Reports (CLIR – 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

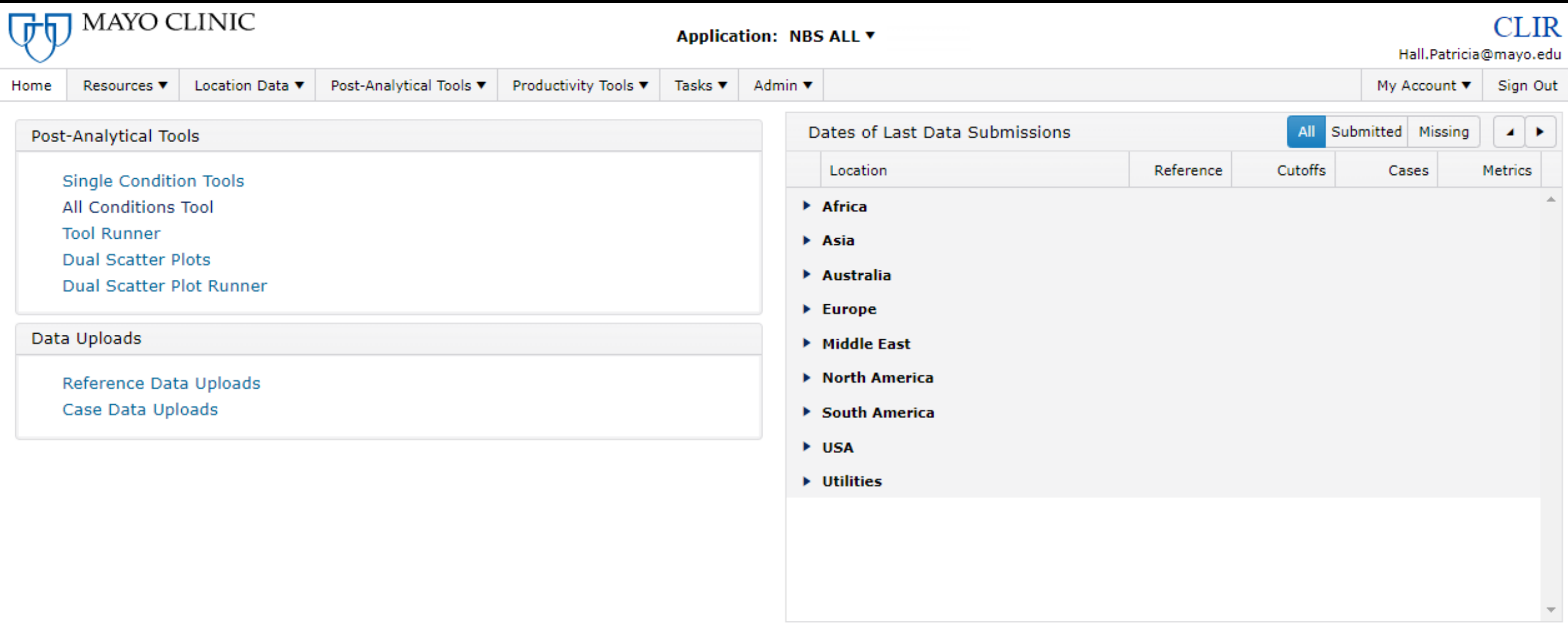
SPECIFICITY IN NEWBORN SCREENING (NBS)

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?



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

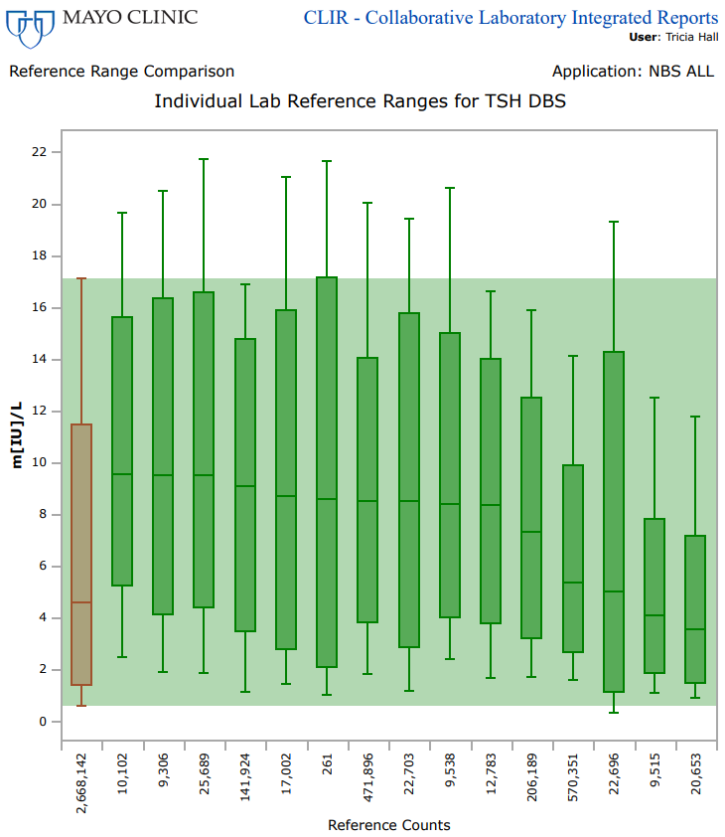
- CLIR is a Mayo Clinic backed endeavor
- Collects full profiles of cases, controls and false positives
- Adjustment of submitted data for covariates and location – continuous rather than discrete reference range bins
- Submission of data required for participation

IMPROVING SPECIFICITY WITH CLIR

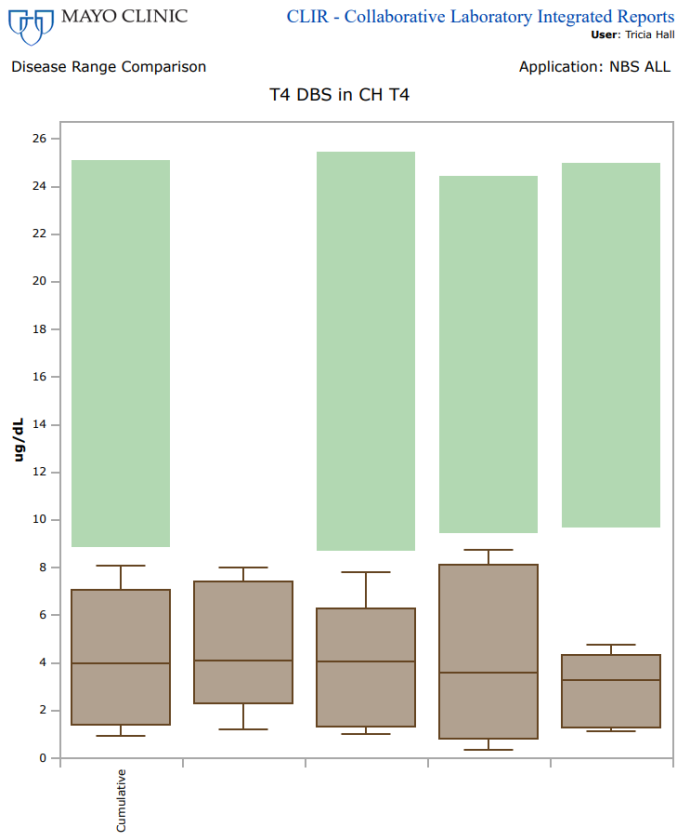
- Multifaceted approach, none of it is passive
  - Data evaluation
    - Provides visual examination of your data against those of other labs
    - Spot check of analytical performance (do you have a fussy analyte?)
  - Algorithm refinement & marker identification
    - Potential to evolve from single 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

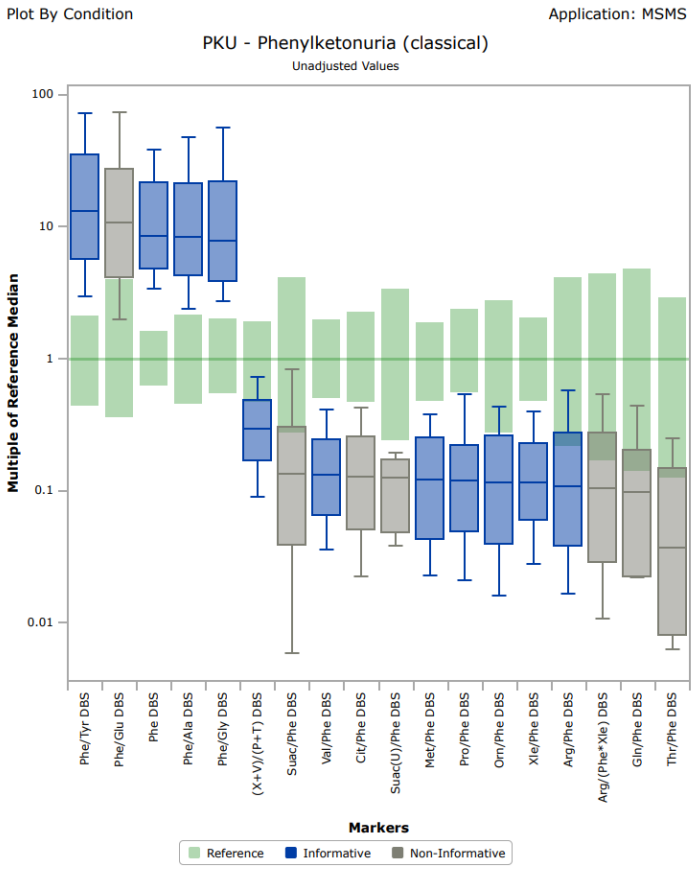


- Once data have been submitted, can compare (anonymously) to peer labs
- Available for reference data and targeted conditions

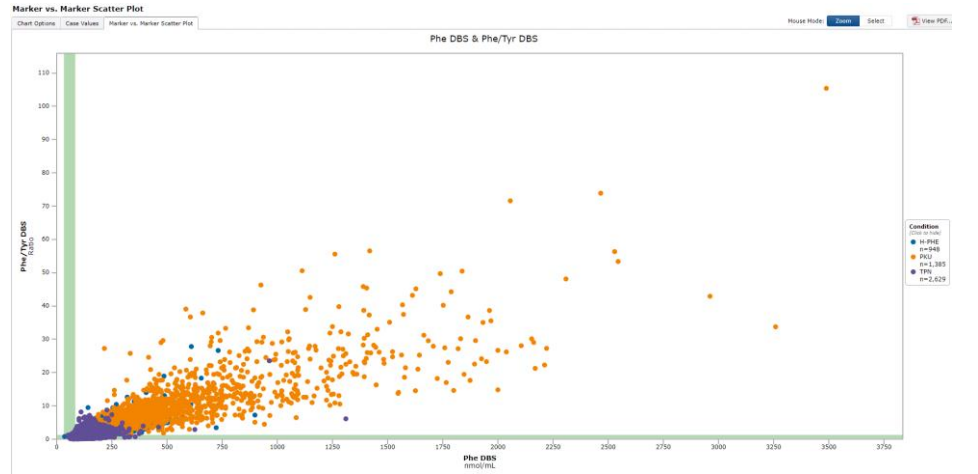


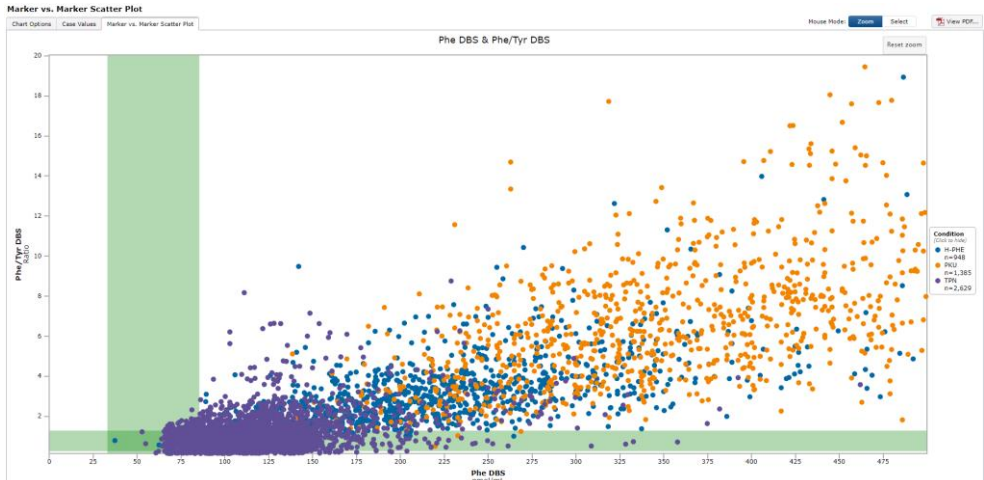
ALGORITHM REFINEMENT

- 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
Covariates		
BW	3200	>=250 and <=10000
Age hr	24	>0 and <=10000
Informative Low Markers		
GAA-MS DBS	1.21	nmol/mL/hr
Differentiator Markers		
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

MAYO CLINIC — CLIR - Collaborative Laboratory Integrated Reports

User: Tricia Hall
Case ID: User Entered

Tool: Pompe 029 — Application: LSD6

Case Score

All	MAYO	RST
331	303	303

%ile Rank of all Pompe Scores

67	64	64

Count of Pompe Scores

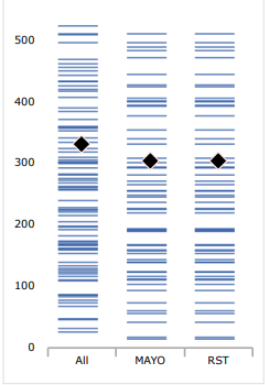
98	65	65

Score Interpretation Guidelines

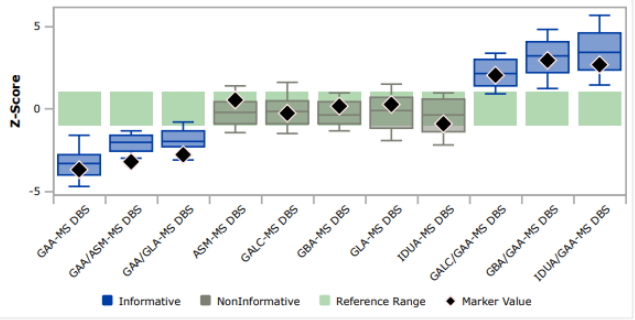
Score is	Interpretation
>= 290	Condition is very likely Pompe
>= 110 and < 290	Condition is likely Pompe
>= 5 and < 110	Condition is possibly Pompe. For a score in this range or higher, consider performing the second tier test for the (Cre/Cm)/GAA ratio.
< 5	Profile is not informative for Pompe

Post-analytical tools are intended to assist in the interpretation of laboratory results, and are not meant to be a substitute for professional judgment. All guidelines, interpretations, figures and calculations must be confirmed by qualified healthcare professionals before clinical use.

Score Ranges

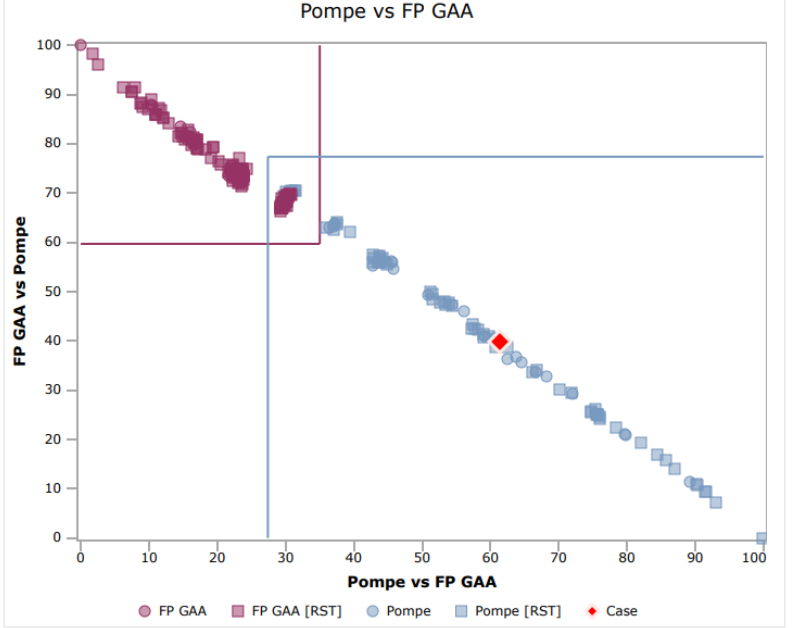


Reference Percentiles and Disease Range Overlap Plot



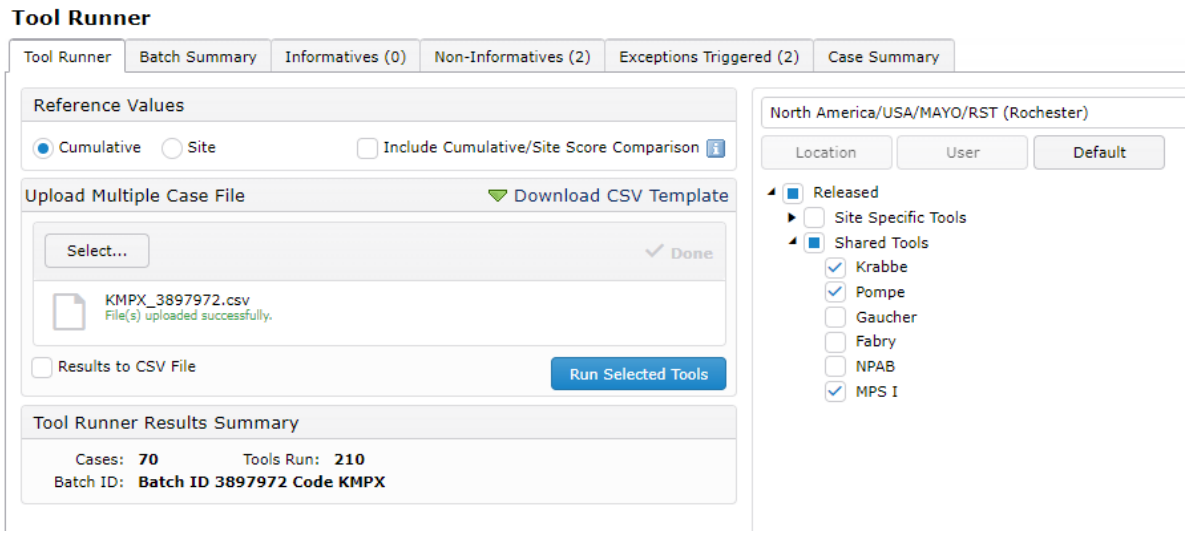
Tool: Pompe vs FP GAA 025 — Application: LSD6

Dual Scatter Plot

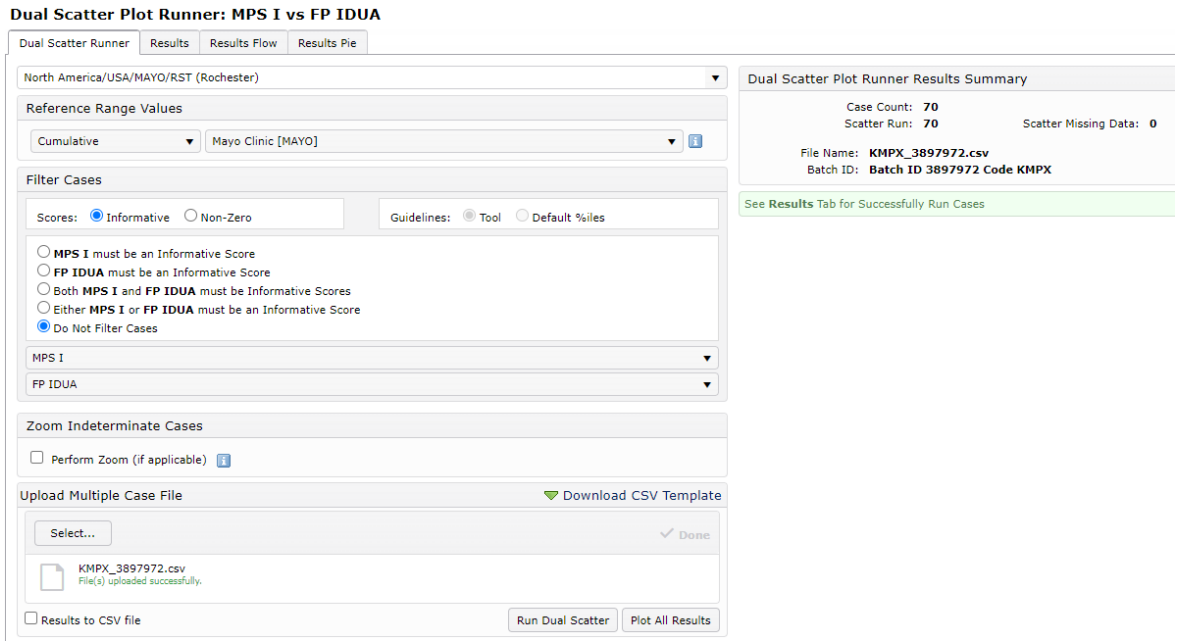


INTEGRATION INTO LABORATORY WORKFLOW

- Tool runner
- Dual scatter plot runner



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



- 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
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- Organizing Committee

QUESTIONS & ANSWERS