Precision Newborn Screening driven by Adjustment of Results for Multiple Covariates

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11th ISNS EUROPEAN REGIONAL MEETING
Bratislava, Slovakia

October 15th, 2018

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Outline

- Introduction to CLIR
- Result adjustments for continuous and categorical covariates, & location
- The RUST (the RUSP post-analytical tool)
- Precision newborn screening workflow
- Examples of performance (LSD, CH, CF)

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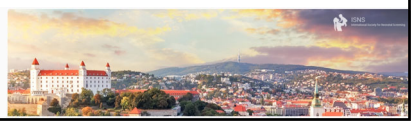

2

Outline

- Introduction to CLIR

11th ISNS EUROPEAN REGIONAL MEETING
Bratislava, Slovakia

3

Collaborative Laboratory Integrated Reports (CLIR)

- CLIR is a multivariate pattern recognition software and interactive web tool that was initially developed to support Region 4 Stork (R4S), a federally-funded (2004-2012) collaborative project for laboratory quality improvement of newborn screening by tandem mass spectrometry

World

FINAL Status of R4S (August 31st, 2018)

Countries	69
Locations (programs)	269
Registered active users	1,206
Positive cases (94 conditions)	20,938
Final count of website user logins	160,759
Final count of website page views	1,607,321
Newborns tested in R4S (2012-2018)	28,726,855
Calculated post-analytical tool scores	411,746,680

4

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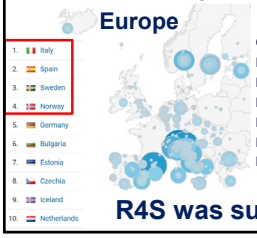
Europe



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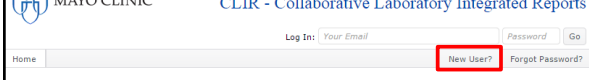
R4S was sunset on Sep. 25th, 2018

5

Collaborative Laboratory Integrated Reports (CLIR)

- CLIR is a multivariate pattern recognition software and interactive web tool that was initially developed to support Region 4 Stork (R4S), a federally-funded (2004-2012) collaborative project for laboratory quality improvement of newborn screening by tandem mass spectrometry
- Since 2012, CLIR is supported by institutional funding and has been approved as an official product of Mayo Clinic



https://clir.mayo.edu

6

Collaborative Laboratory Integrated Reports (CLIR)

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- Since 2012, CLIR is supported by institutional funding and has been approved as an official product of Mayo Clinic
- (Mayo letter to NICHD, Sept. 2014) ….. CLIR will remain freely available to all interested users in perpetuity when applications are related to newborn screening, clinical biochemical genetics, and pediatric medicine in general

7

Collaborative Laboratory Integrated Reports (CLIR)

- CLIR is a multivariate pattern recognition software and interactive web tool that was initially developed to support Region 4 Stork (R4S), a federally-funded (2004-2012) collaborative project for laboratory quality improvement of newborn screening by tandem mass spectrometry

CLIR is free….
but contribution of data is *required*

- (Mayo letter to NICHD, Sept. 2014) ….. CLIR will remain freely available to all interested users in perpetuity when applications are related to newborn screening, clinical biochemical genetics, and pediatric medicine in general

8

What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous covariate-adjusted %iles
- Replaces analyte cutoff values
  - With condition-specific disease ranges
- Enhances the clinical utility of individual markers
  - With all possible permutation of ratios
- Replaces diagnostic sequential algorithms (“and”)
  - With tool-based parallel algorithms (“or”)

9

What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous covariate-adjusted %iles

10

Outline

- Introduction to CLIR
- Result adjustments for continuous and categorical covariates, & location

11

Standard Data Collection

- Date and time (hh:mm) of birth
- Date and time of sample collection

Birth Date (MM DD, YYYY)	Birth Time	
10/13/2018	5:37	X A.M. ☐ P.M.

48h?

Collection Date (MM, DD, YYYY)	Collection Time	
10/15/2018	2:45	☐ A.M. X P.M.

72h?

12

Standard Data Collection

- Date and time (hh:mm) of birth
- Date and time of sample collection

Birth Date (MM DD, YYYY)	Birth Time
10/13/2018	5:37 ☒A.M. ☐P.M.

Collection Date (MM, DD, YYYY)	Collection Time
10/15/2018	2:45 ☐A.M. ☒P.M.

= PRECISE Age at collection (hours)

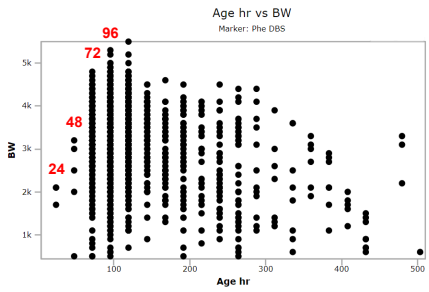
57.1333

Are decimal digits *really* necessary?

13

First Submission

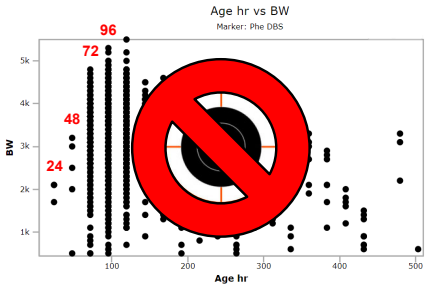
First submission	Age hr
Case ID	35659-2
18-215180	24
18-225344	24
18-225345	24
18-225346	48
18-206225	48
18-222109	48
18-211369	48
18-232052	48
18-208134	72
18-207172	72
18-232336	72
18-213209	72
18-212387	72
18-219603	96
18-211227	96
18-228169	96
18-226356	96
18-211380	96



14

First Submission (Rejected)

First submission	Age hr
Case ID	35659-2
18-215180	24
18-225344	24
18-225345	24
18-225346	48
18-206225	48
18-222109	48
18-211369	48
18-232052	48
18-208134	72
18-207172	72
18-232336	72
18-213209	72
18-212387	72
18-219603	96
18-211227	96
18-228169	96
18-226356	96
18-211380	96



Narrow, high density data "stripes" cause significant noise and possibly errors in the calculation of the regression model

15

Standard Data Collection

- Date and time (hh:mm) of birth
- Date and time of 2nd sample collection

Birth Date (MM DD, YYYY)	Birth Time
10/13/2018	5:37 ☒A.M. ☐P.M.

Collection Date (MM, DD, YYYY)	Collection Time
10/27/2018	9:00 ☒A.M. ☐P.M.

= PRECISE Age at collection (hours)

339.3833

NBS Demographic information	
	Age hr
Case ID	35659-2
181015-0265	57.1333
181027-0030	339.3833

16

Standard Data Collection

- Date and time (hh:mm) of birth
- Date and time of 2nd sample collection

Birth Date (MM DD, YYYY)	Birth Time
10/13/2018	5:37 ☒A.M. ☐P.M.

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10/27/2018	9:00 ☒A.M. ☐P.M.

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339.3833

NBS Demographic information		
	Age hr	
Case ID	35659-2	????
181015-0265	57.1333	
181027-0030	339.3833	

Logical Observation Identifiers Names and Codes

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LOINC® from Regenstrief (https://loinc.org)

The universal standard for identifying health measurements, observations, and documents.

Reference labs, healthcare organizations, U.S. federal agencies, insurance companies, software vendors, *in vitro* diagnostic testing companies, and more than 69,000 registered users from 172 countries use LOINC to move data seamlessly between systems.

It's free, but invaluable.

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LOINC from Regenstrief (https://loinc.org)

LOINC Code Information

LOINC Number	**35659-2**
	The unique LOINC Code is a string in the format of nnnnnnnn-n.
Component	**AGE AT SPECIMEN COLLECTION**
	First major axis-component or analyte
Property	**TIME**
	Second major axis-property observed (e.g., mass vs. substance)
Time Aspect	**PT**
	Third major axis-timing of the measurement (e.g., point in time vs 24 hours)
System	**^PATIENT**
	Fourth major axis-type of specimen or system (e.g., serum vs urine)
Scale Type	**QN**
	Fifth major axis-scale of measurement (e.g., qualitative vs. quantitative)

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LOINC from Regenstrief (https://loinc.org)

Improving newborn screening laboratory test ordering and result reporting using health information exchange

Stephen M Downs,[1] Peter C van Dyck,[2] Piero Rinaldo,[3] Clement McDonald,[4] R Rodrey Howell,[5] Alan Zuckerman,[6] Gregory Downing[7]

ABSTRACT

Capture, coding and communication of newborn screening (NBS) information represent a challenge for public health laboratories, health departments, hospitals, and ambulatory care practices. An increasing number of conditions targeted for screening and the complexity of interpretation contribute to a growing need for integrated information-management strategies. This makes NBS an important test of tools and architecture for electronic health information exchange (HIE) in this convergence of individual patient care and population health activities. For this reason, the American Health Information Community undertook three tasks described in this paper. First, a newborn screening use case was established to facilitate standards harmonization for common terminology and interoperability specifications guiding HIE. Second, newborn screening coding and terminology were developed for integration into electronic HIE activities. Finally, clarification of privacy, security, and clinical laboratory regulatory requirements governing information exchange was provided, serving as a framework to establish pathways for improving screening program timeliness, effectiveness, and efficiency of quality patient care services.

[1]Children's Health Services Research Program, Indiana University School of Medicine, Indianapolis, Indiana, USA [2]Department of Health and Human Services, Health Resources and Services Administration, Washington, DC, USA [3]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA [4]Department of Health and Human Services, The Lister Hill Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA [5]Department of Health and Human Services, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA [6]Georgetown University Medical Center, Washington, DC, USA [7]Department of Health and Human Services, Personalized Health Care Initiative, Washington, DC, USA

J Am Med Inform Assoc 2010;**17**:13–18. doi:10.1197/jamia.M3295

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Standard Data Collection

- **Birth weight** (grams)
- **Gestational age** (weeks)
- **Sex** (Male/Female)

Birth Weight (grams)	Gestational Age (wks.)	Gender
2957	39.1	☐ M ☒ F

NBS Demographic information

	Age hr	BW	GA (wk)	Sex
Case ID	35659-2	56056-5	49051-6	46098-0
181015-0265	57.1333	2957	39.1	Female
181027-0030	339.3833	2957	39.1	Female

21

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- **Birth weight** (grams)
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- **Sex** (Male/Female)

Birth Weight (grams)	Gestational Age (wks.)	Gender
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	Age hr	BW	GA (wk)	Sex
Case ID	35659-2	56056-5	49051-6	46098-0
181015-0265	57.1333	2957	39.1	Female
181027-0030	339.3833	2957	39.1	Female

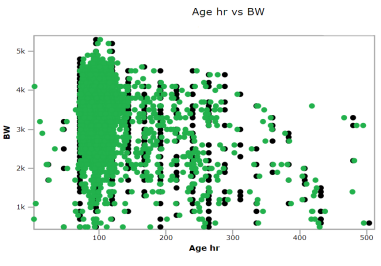
NO PHI

22

Second Submission (Accepted)

Second submission

Case ID	Age hr
	35659-2
18-206013	233.25
18-206014	263.78
18-206015	260.3
18-206016	191.58
18-206017	277.58
18-206018	96.27
18-206020	93.92
18-206021	111.85
18-206022	107.52
18-206023	112.85
18-206024	86.35
18-206026	82.45
18-206027	95.42
18-206029	102.97
18-206030	94.42
18-206031	110.27
18-206032	80.45
18-206033	104.78



23

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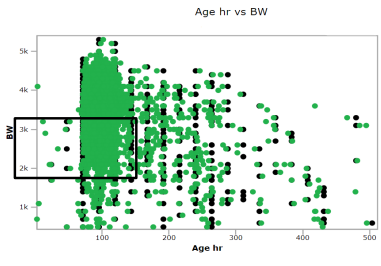
18-206022	107.52
18-206023	112.85
18-206024	86.35
18-206026	82.45
18-206027	95.42
18-206029	102.97
18-206030	94.42
18-206031	110.27
18-206032	80.45
18-206033	104.78

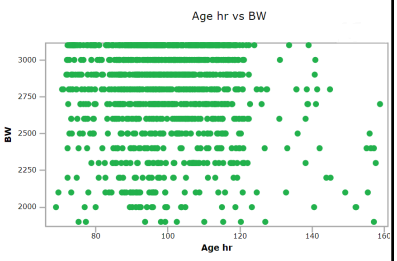


Reluctantly……

24

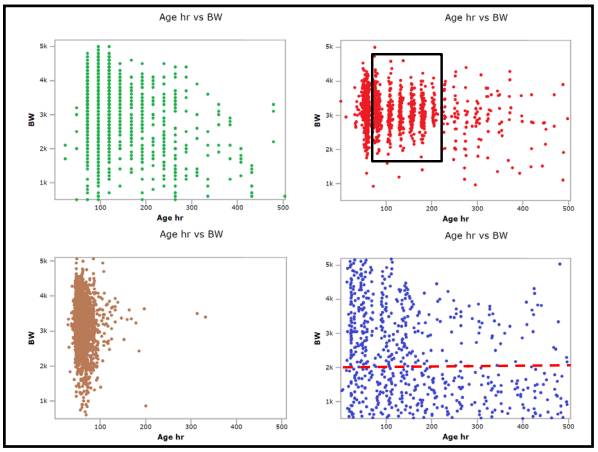
Second Submission (Accepted)

Second submission	Age hr	BW
Case ID	35659-2	56056-5
18-206013	233.25	3900
18-206014	263.78	3200
18-206015	260.3	2200
18-206016	191.58	4000
18-206017	277.58	4400
18-206018	96.27	2900
18-206020	93.92	500
18-206021	111.85	2800
18-206022	107.52	3900
18-206023	112.85	3400
18-206024	86.35	3000
18-206026	82.45	3700
18-206027	95.42	3700
18-206029	102.97	3200
18-206030	94.42	2800
18-206031	110.27	4100
18-206032	80.45	4500
18-206033	104.78	4300



Reluctantly……

25



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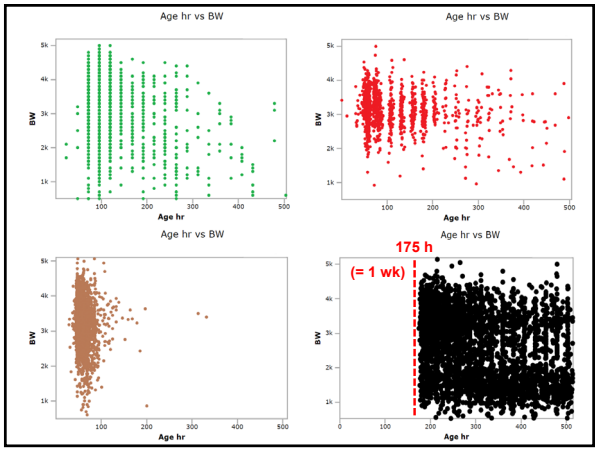
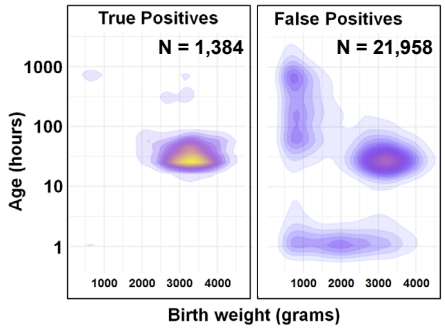


27

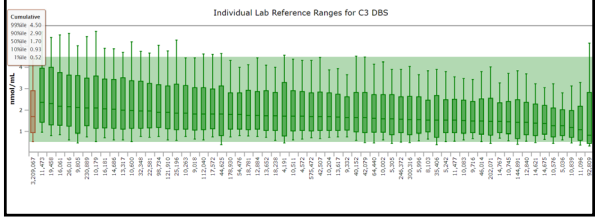
Covariate Density Plot of Congenital Hypothyroidism



28

Propionylcarnitine (C3) as Model Marker

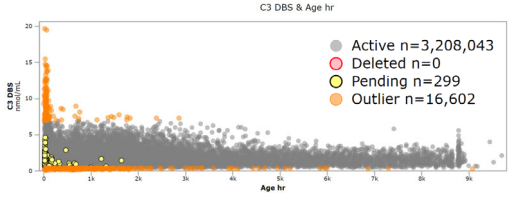
- 62 contributing locations (5k to 575k)
- Cumulative data count: 3,209,067



29

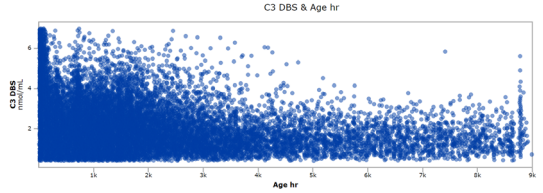
Propionylcarnitine (C3) as Model Marker

- 62 contributing locations (5k to 575k)
- Cumulative data count: 3,209,067
- Outliers (excluded) 16,602



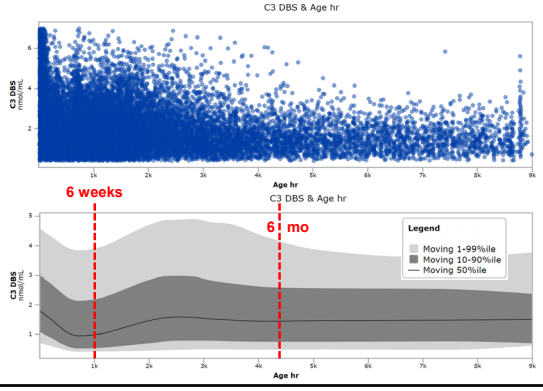
30

Marker vs. Covariate Plot



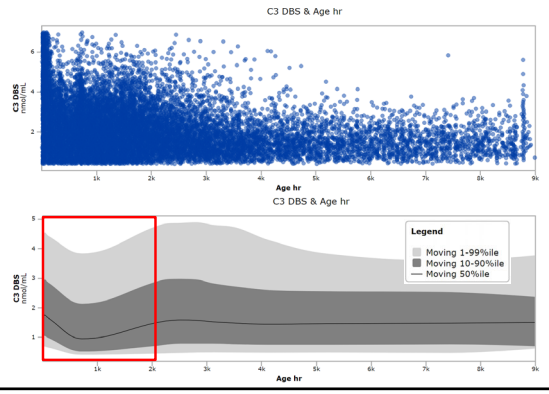
31

Continuous Moving Percentiles?



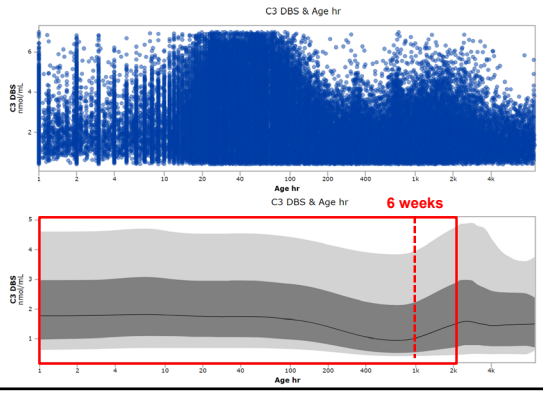
32

Continuous Moving Percentiles?



33

Marker vs. Covariate Plot (LOG)



34

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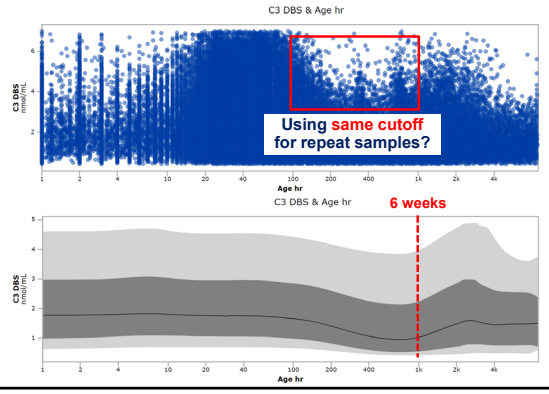

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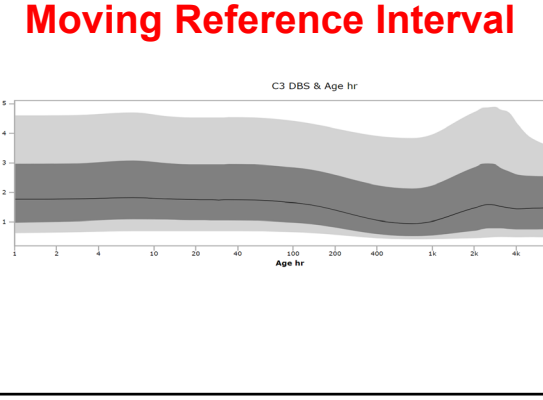
Continuous (Unadjusted) Moving Reference Interval



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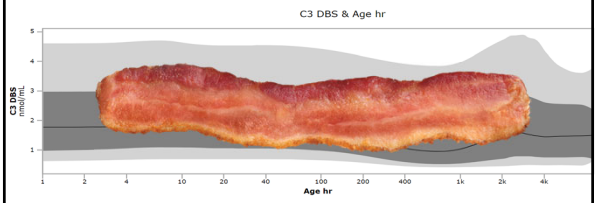
a.k.a. The BACON Plot



Where is this coming from?

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Clinical Chemistry 61:5
760-768 (2015)

Informatics and Statistics

Continuous Age- and Sex-Adjusted Reference Intervals of Urinary Markers for Cerebral Creatine Deficiency Syndromes: A Novel Approach to the Definition of Reference Intervals

Lars Mørkrid,[1] Alexander D. Rowe,[1] Katja B.P. Elgstoen,[1] Jess H. Olesen,[2] George Ruijter,[3] Patricia L. Hall,[4] Silvia Tortorelli,[5] Andreas Schulze,[6] Lianna Kyriakopoulou,[7] Mirjam M.C. Wamelink,[8] Jiddeke M. van de Kamp,[9] Gajja S. Salomons,[8] and Piero Rinaldo[5]

Oslo University Hospital

38

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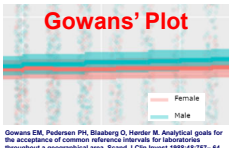
39

Does Propionylcarnitine (C3) Need an Adjustment for SEX?

Gowans' Plot



Gowans EM, Pedersen PH, Blaaberg O, Harder M. Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area. Scand J Clin Invest 1988;48:757– 64.

Male median ± ¼ SD
vs.
Female median ± ¼ SD

If the two bands overlap for the whole range of the covariate (no separation) there is no need to establish separate reference intervals by sex

40

Does Propionylcarnitine (C3) Need an Adjustment for SEX?

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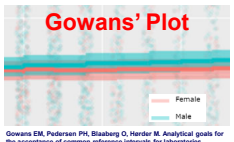

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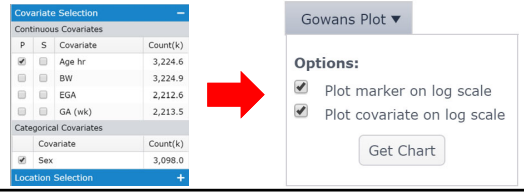

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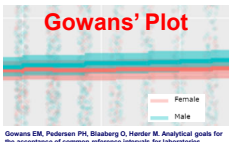
Does Propionylcarnitine (C3) Need an Adjustment for SEX?

Gowans' Plot



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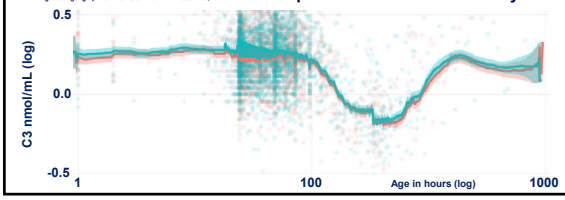
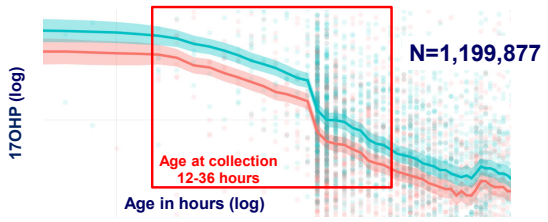
Female median ± ¼ SD

If the two bands overlap for the whole range of the covariate (no separation) there is no need to establish separate reference intervals by sex



42

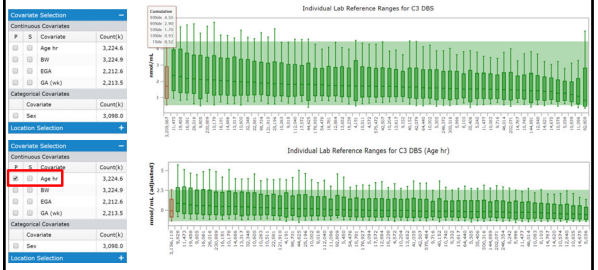
The Gowans' Plot of 17-Hydroxy Progesterone (17OHP)



More later, now back to C3

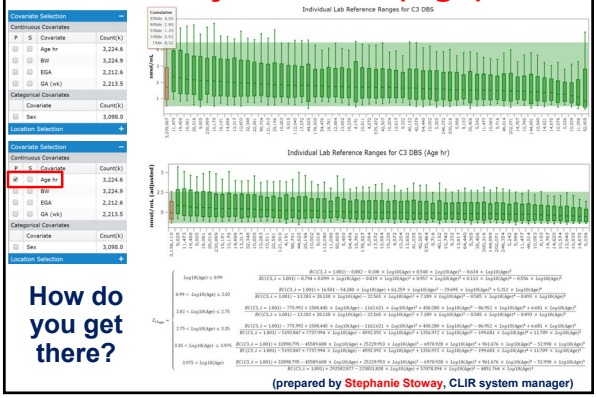
43

C3 Adjustments (Age)



44

C3 Adjustments (Age)



How do you get there?

(prepared by Stephanie Stoway, CLIR system manager)

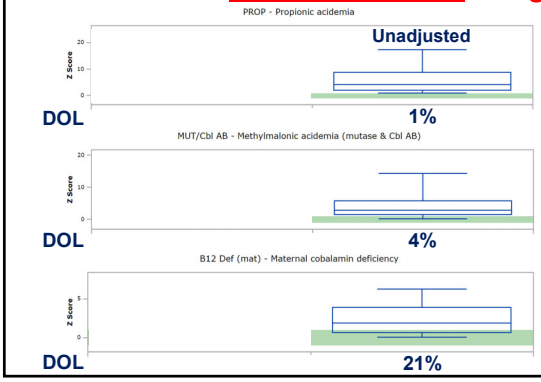
45

What Does CLIR DO, Exactly?

- **Replaces conventional reference ranges**
  - **With continuous covariate-adjusted %iles**
- **Replaces analyte cutoff values**
  - **With condition-specific disease ranges**

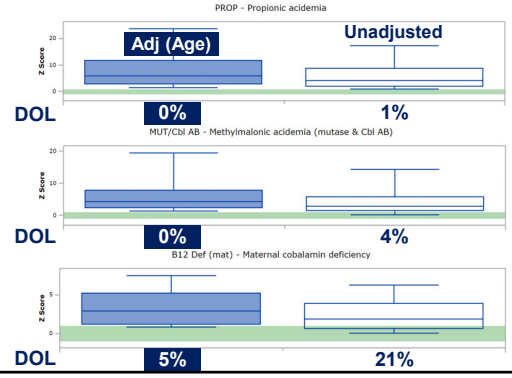
46

C3 Degree of Overlap (DOL) between Reference and Disease-Specific Ranges



47

C3 Degree of Overlap (DOL) between Reference and Disease-Specific Ranges



48

What Difference Does it Make?

A JOURNAL SENTINEL SPECIAL REPORT

The price of being wrong

Newborn screening saves babies, but lives can be shattered when state labs ignore science and common sense.

By Ellen Gabler of the Milwaukee Journal Sentinel

Dec. 9, 2016

http://projects.jsonline.com/news/2016/12/11/the-price-of-being-wrong.html

49

What Difference Does it Make?

A JOURNAL SENTINEL SPECIAL REPORT

The price of being wrong

Newborn screening saves babies, but lives can be shattered when state labs ignore science and common sense.

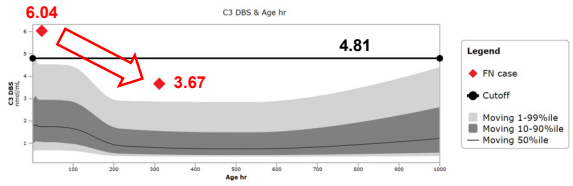
The story of Jonathan Page

Jonathan needed a retest from a new blood sample. By now, he was two weeks old. The baby seemed healthy, but his mom brought him to the doctor to have more blood collected. A week later his pediatrician received the follow-up report: *Normal.*

http://projects.jsonline.com/news/2016/12/11/the-price-of-being-wrong.html

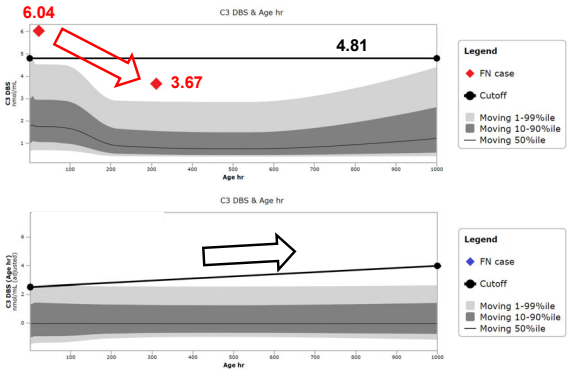
50

C3 Results of Jonathan Page



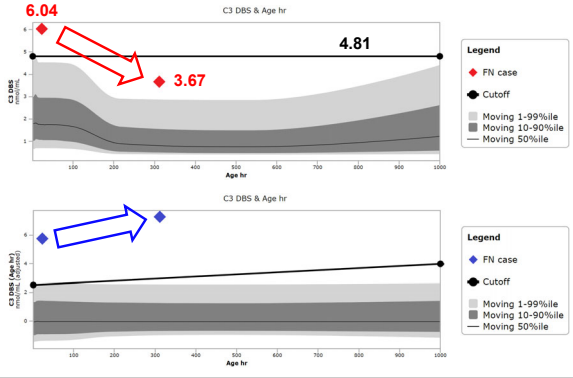
51

C3 Results of Jonathan Page



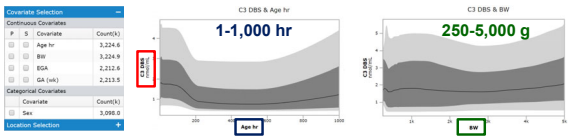
52

C3 Results of Jonathan Page



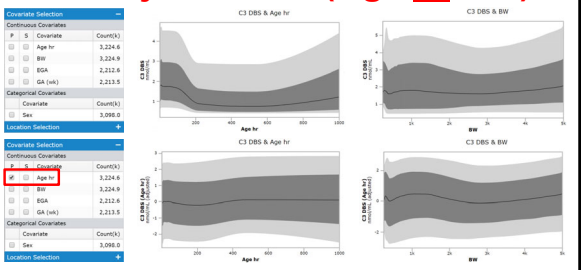
53

C3 Adjustments (Age or BW)



54

C3 Adjustments (Age or BW)



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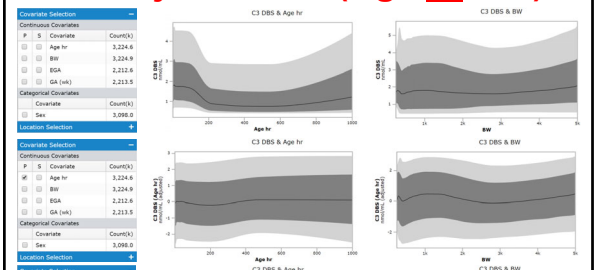
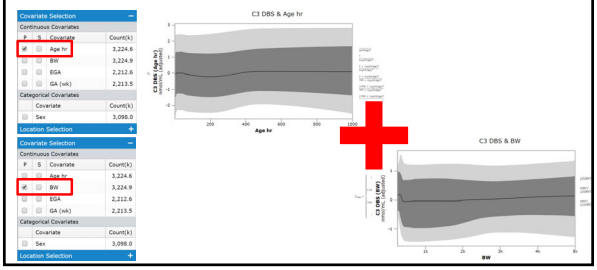
C3 Adjustments (Age or BW)



56

C3 Adjustments (Age or BW)



57

C3 Adjustments (Age or BW)

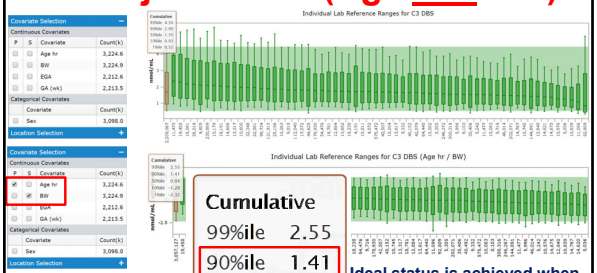
58

C3 Adjustments (Age and BW)

What does it mean?

59

C3 Adjustments (Age and BW)



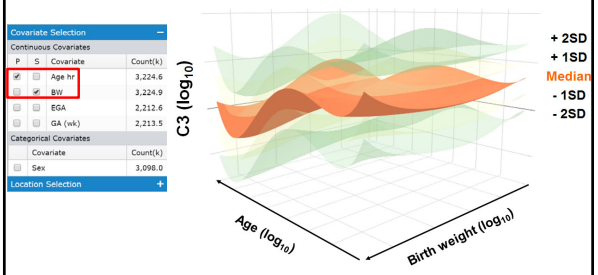
How does it look?

Cumulative	
99%ile	2.55
90%ile	1.41
50%ile	0.04
10%ile	-1.28
1%ile	-2.32

Ideal status is achieved when
90%ile is = 1.28
50%ile is = 0.00
10%ile is = -1.28
These parameters mean that 80% of the data are within ± 1 SD (std. dev.)

60

Continuous Moving Reference Range of C3 Adjusted for AGE and BW



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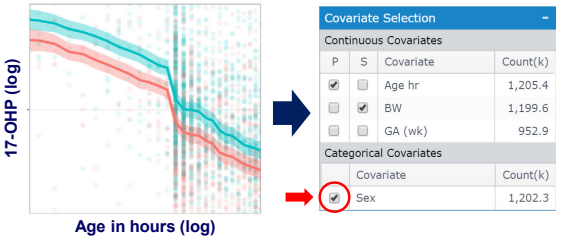
Continuous Moving Reference Range of 17OHP Adjusted for AGE and BW and SEX



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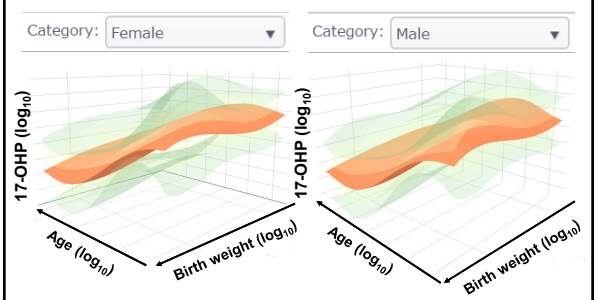
Reference Ranges for 17OHP Adjusted for AGE & BW & SEX



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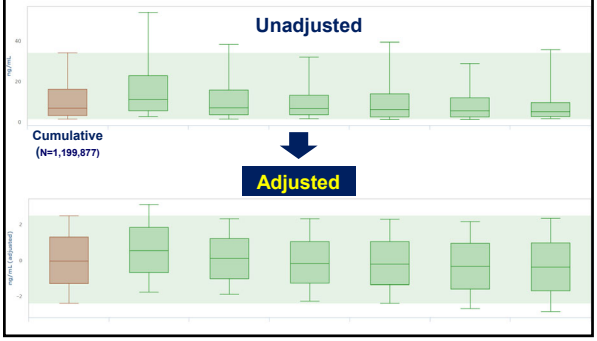
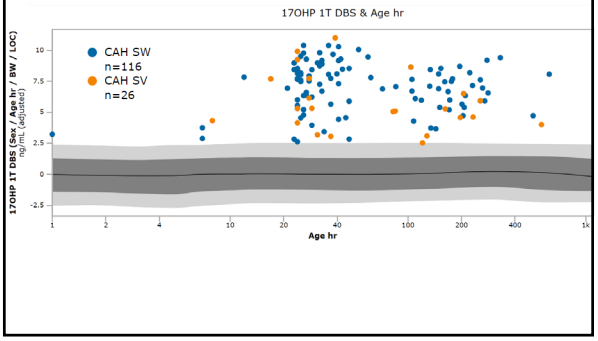
Reference Ranges for 17OHP Adjusted for AGE/BW/SEX/LOC



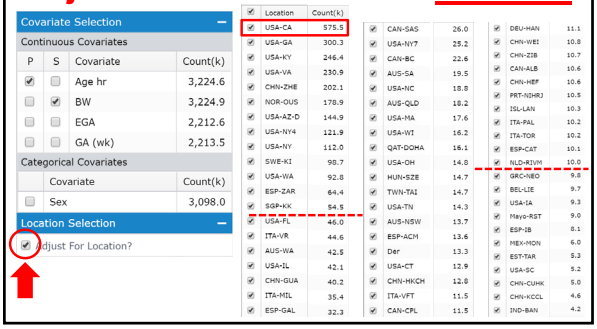
64

Reference Ranges for 17OHP Adjusted for AGE/BW/SEX/LOC



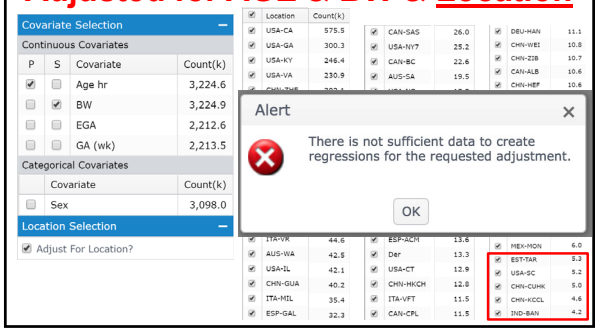
65

Continuous Moving Reference Range of C3 Adjusted for AGE & BW & Location



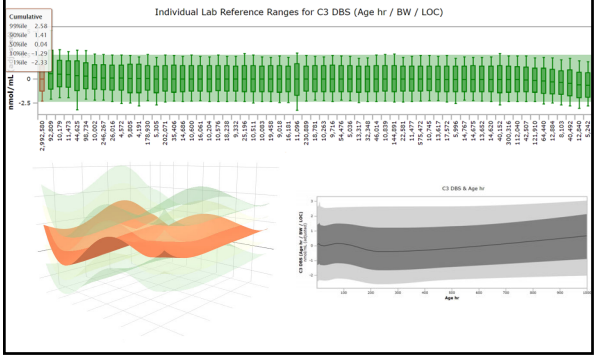
66

Continuous Moving Reference Range of C3 Adjusted for AGE & BW & Location



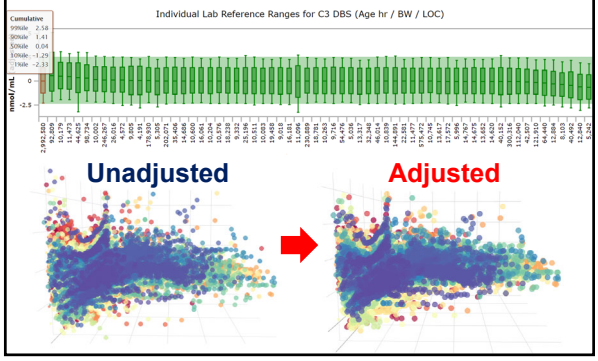
67

Propionylcarnitine (C3) Adjusted for Age / BW / Location



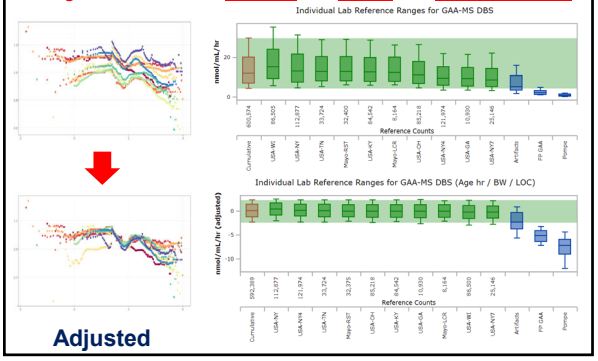
68

Propionylcarnitine (C3) Adjusted for Age / BW / Location



69

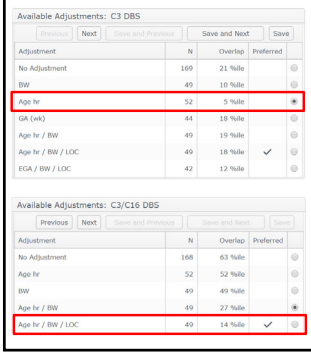
Reference Ranges for GAA (Pompe) Adjusted for AGE & BW & Location



70

What Difference Does It Make?

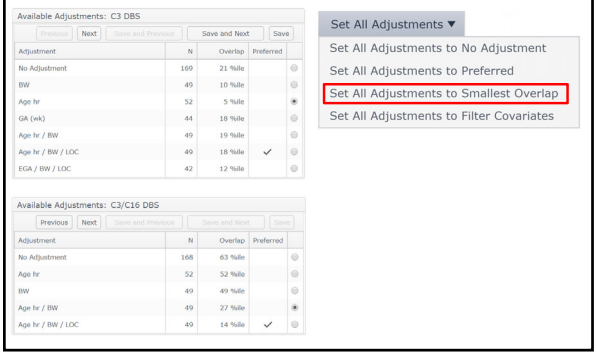
Condition: **B12 Def (mat)**



71

What Difference Does It Make?

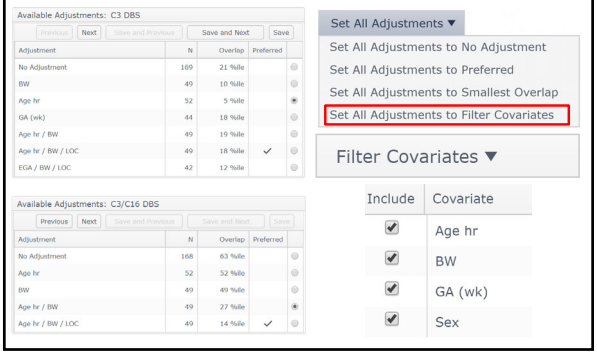
Condition: **B12 Def (mat)**



72

What Difference Does It Make?

Condition: **B12 Def (mat)**



73

Outline

- Introduction to CLIR
- Result adjustments for continuous / categorical covariates, and location
- The RUST (the RUSP post-analytical Tool)

74

Recommended Uniform Screening Panel

- 35 primary conditions
  - 20 IEM detected by MS/MS (AA FAO OA)
  - 2 endocrine disorders (CH CAH)
  - 3 Hemoglobinopathies (S/S, S/βThal, S/C)
  - 2 Lysosomal disorders (Pompe MPS I)
  - 8 others (BIOT CF GALT HEAR SCID CCHD X-ALD SMA)
- 27 secondary targets
  - 22 IEM detected by MS/MS (AA, FAO, OA)
  - 1 Hemoglobinopathy (many variants counted as 1)
  - 4 others (GAL-epimerase, GAL-kinase, other T-cell def., DPB)

75

Recommended Uniform Screening Panel

29 primary conditions

- 20 IEM detected by MS/MS (AA FAO OA)
- 2 endocrine disorders (CH CAH)
- 2 Lysosomal disorders (Pompe MPS I)
- 5 others (BIOT CF GALT SCID X-ALD)

76

Primary Markers of 29 Target Conditions

- Amino acids (5)
  - Cit, Xle, Met, Phe, Tyr
- Acylcarnitines (8)
  - C0, C3, C5, C5OH, C8, C5DC, C14:1, C16OH
- Lysosomal enzymes (2)
  - GAA, IDUA
- Other markers (7)
  - 17OHP, BIOT, C26, IRT, GALT, TRECS, TSH

77

Additional Markers of Target Conditions

- Amino acids (1)
  - Val
- Acylcarnitines (3)
  - C2, C10, C16
- Lysosomal enzymes (0)
- Other markers (2)
  - C24, T4

78

RUSP Primary Target Conditions with Single Informative Marker

- AA disorders (3/6, 50%)
  - CIT-I, HCY, PKU
- FAO disorders (1/5, 20%)
  - CUD
- OA disorders (6/9, 66%)
  - 3MCC, Cbl AB, GA-I, IVA, MUT, PROP

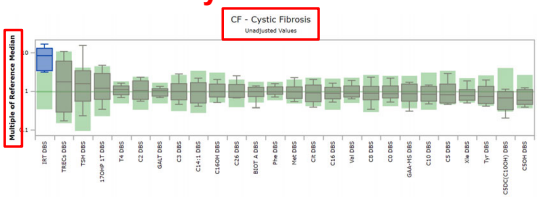
MS/MS 10/20 50%

- Lysosomal disorders (2/2, 100%)
  - Pompe, MPS I
- Other conditions (4/5, 80%)
  - BIOT, CAH, CF, GALT

Others 6/7 86%

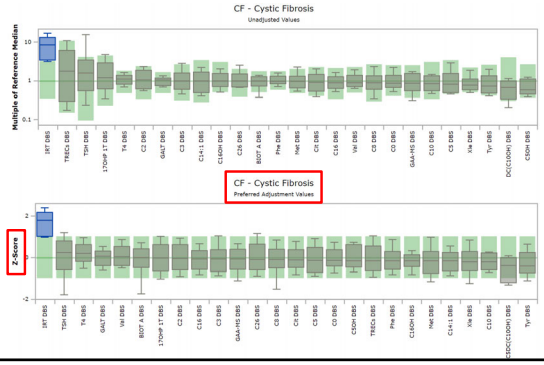
79

Primary RUSP Markers in Cystic Fibrosis



80

Primary RUSP Markers in Cystic Fibrosis



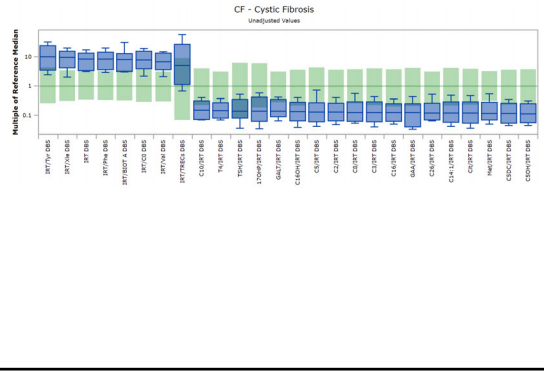
81

What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous covariate-adjusted %iles
- Replaces analyte cutoff values
  - With condition-specific disease ranges
- Enhances the clinical utility of individual markers
  - With all possible permutation of ratios

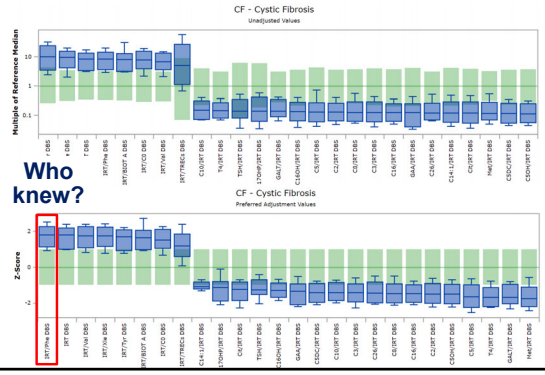
82

Recommended Uniform Screening TOOL for Cystic Fibrosis (IRT + 26 Ratios)



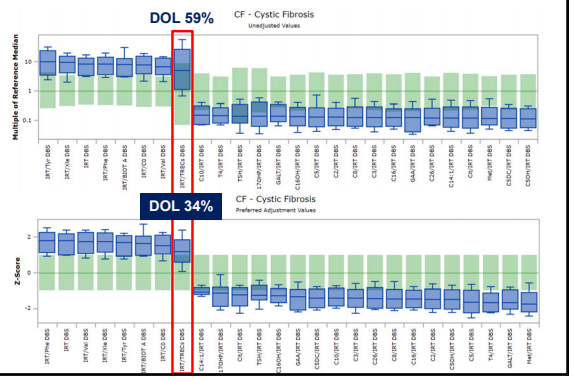
83

Recommended Uniform Screening TOOL for Cystic Fibrosis (IRT + 26 Ratios)



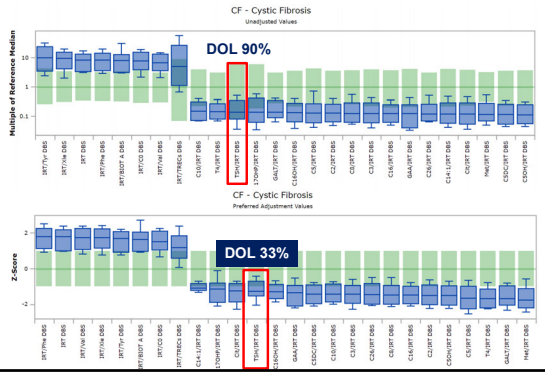
84

Recommended Uniform Screening TOOL for Cystic Fibrosis (IRT + 26 Ratios)



85

Recommended Uniform Screening TOOL for Cystic Fibrosis (IRT + 26 Ratios)



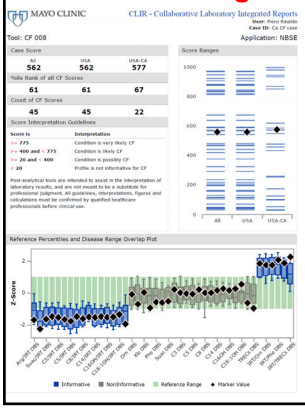
86

What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous covariate-adjusted %iles
- Replaces analyte cutoff values
  - With condition-specific disease ranges
- Enhances the clinical utility of individual markers
  - With all possible permutation of ratios
- Replaces diagnostic sequential algorithms (“and”)
  - With tool-based parallel algorithms (“or”)

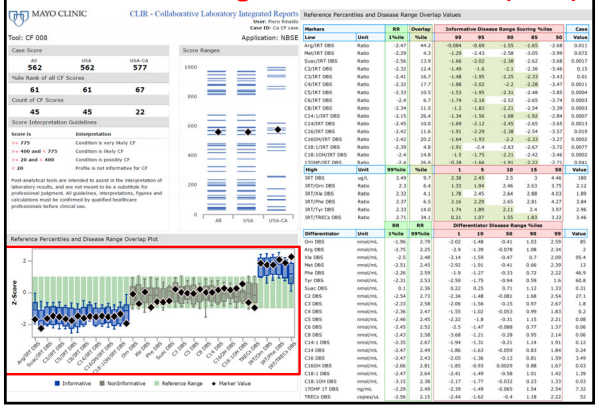
87

USA-CA CF Single Condition Tool (SCT)



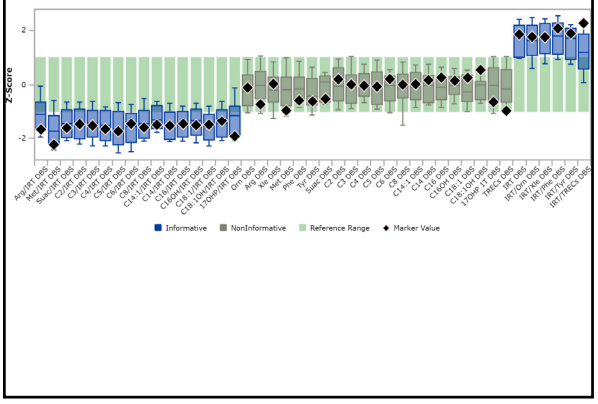
88

USA-CA CF Single Condition Tool (SCT)



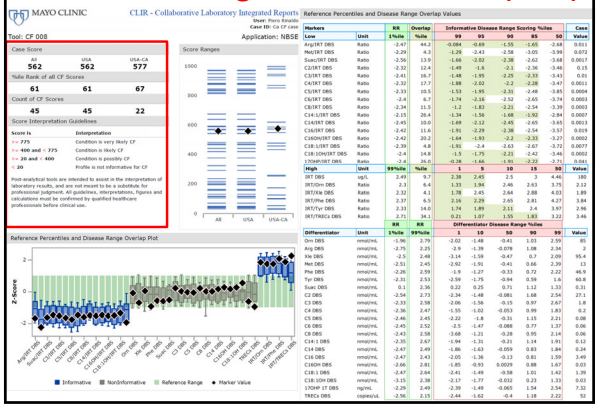
89

USA-CA CF Single Condition Tool (SCT)



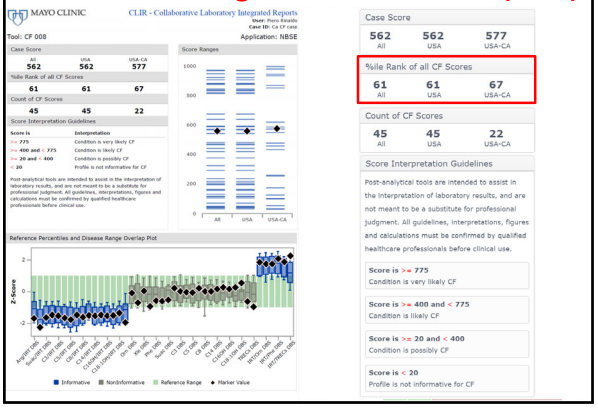
90

USA-CA CF Single Condition Tool (SCT)



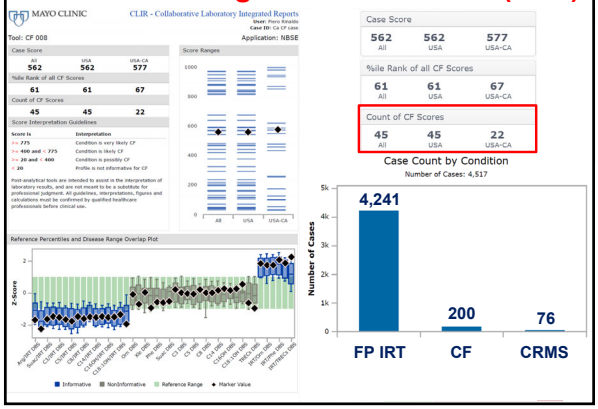
91

USA-CA CF Single Condition Tool (SCT)



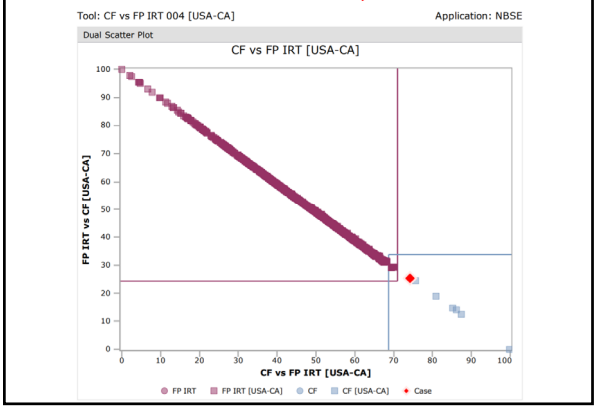
92

USA-CA CF Single Condition Tool (SCT)



93

What Do You Do with >4,000 FP Cases?



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Outline

- Introduction to CLIR
- Result adjustments for continuous / categorical covariates, and location
- The RUST (the RUSP post-analytical tool)
- Precision newborn screening workflow

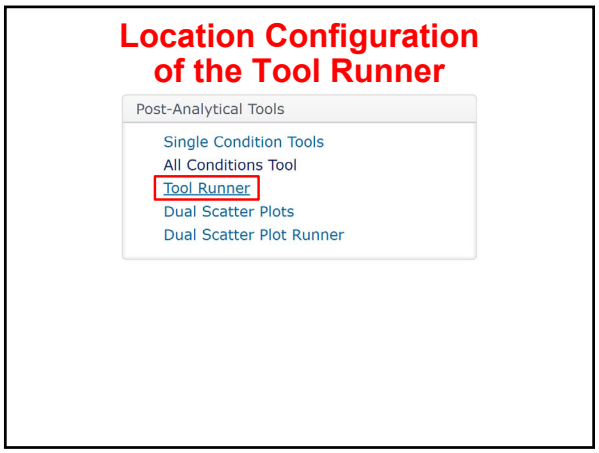
95

Precision NBSE Workflow

- Select conditions on tool runner configuration window
- Preparation and upload csv file
- Run SCT panel (tool runner)
- Run DSP as needed (tool runner)
- Reflex to second tier test, if necessary

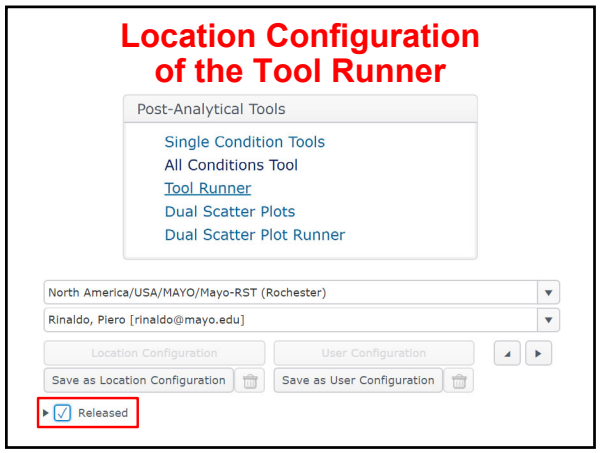
96

Location Configuration of the Tool Runner



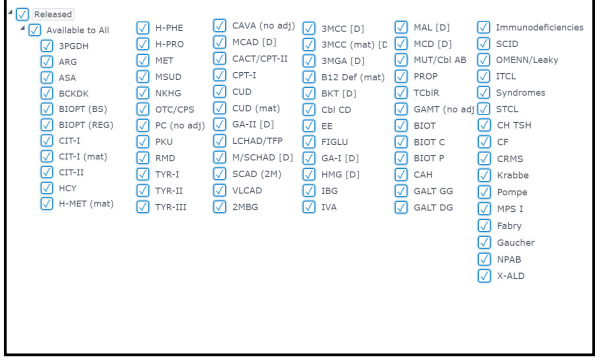
97

Location Configuration of the Tool Runner



98

Location Configuration of the Tool Runner



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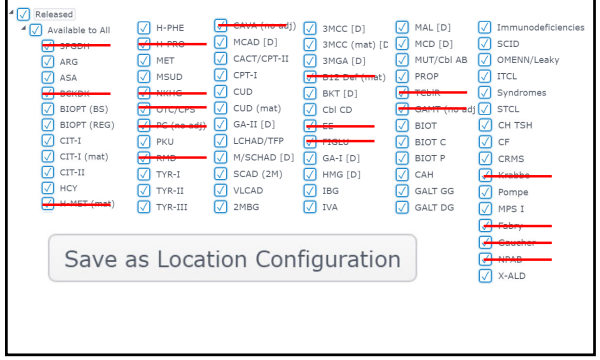
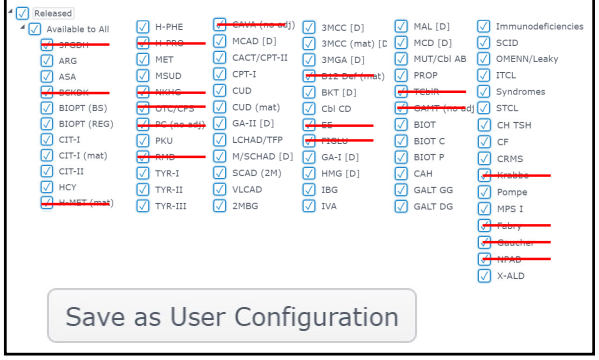
Location Configuration of the Tool Runner



100

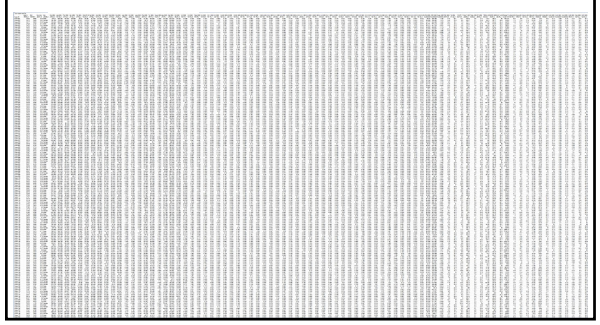
User Configuration of the Tool Runner



101

Preparation of .csv File

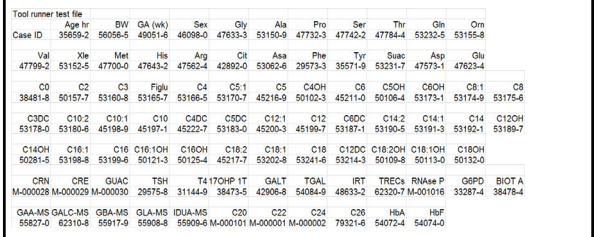
- **175 cases (ISNS TR test file)**



102

Preparation of .csv File

- 175 cases (ISNS TR test file)
  - 4 covariates (700 data points)
  - 81 markers (14,350 data points)



103

Preparation of .csv File

- 175 cases (ISNS TR test file)
  - 4 covariates (700 data points)
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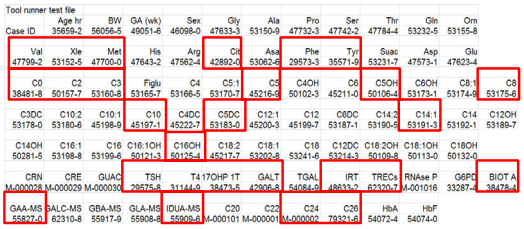

The RUST panel (27/81, 33%)

104

Preparation of .csv File

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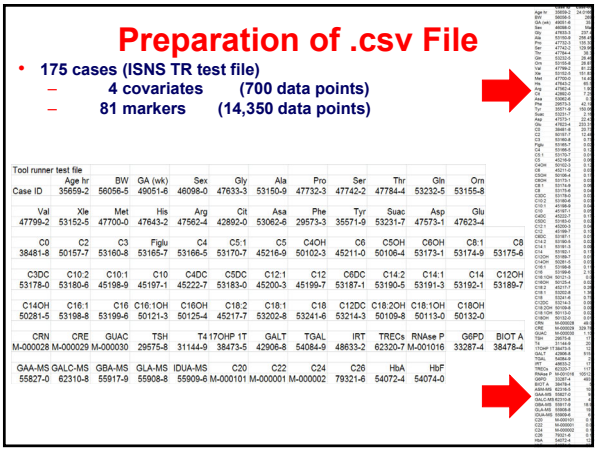
  - 4 covariates (700 data points)
  - 81 markers (14,350 data points)

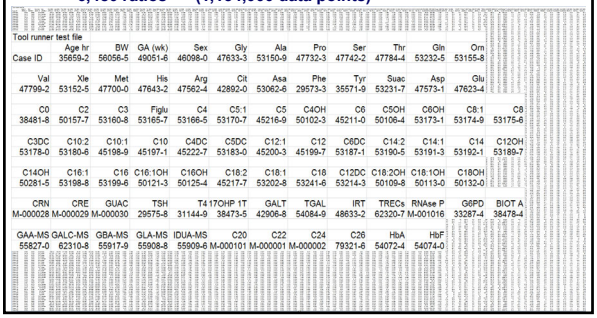


105

Preparation of .csv File

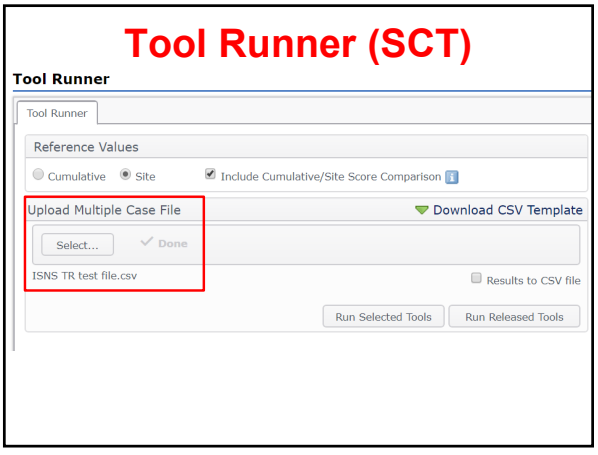
- 175 cases (ISNS TR test file)
  - 4 covariates (700 data points)
  - 81 markers (14,350 data points)
  - 6,480 ratios (1,134,000 data points)

Ratio Explorer



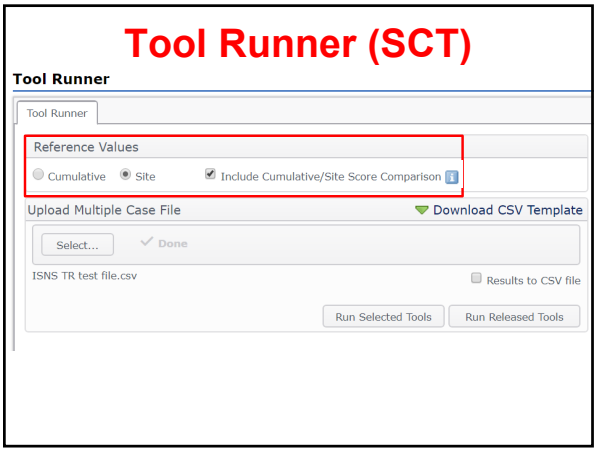
106

Tool Runner (SCT)



107

Tool Runner (SCT)



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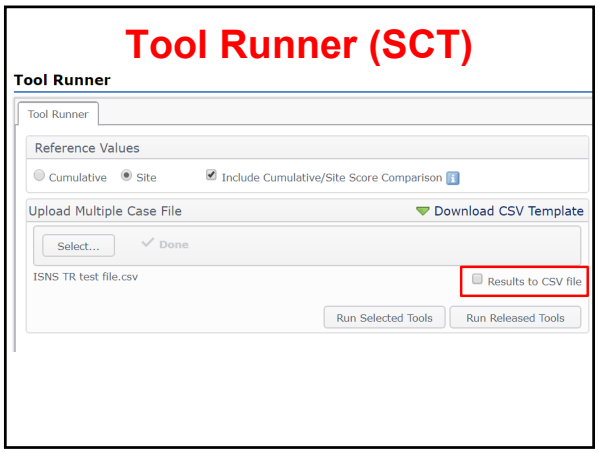

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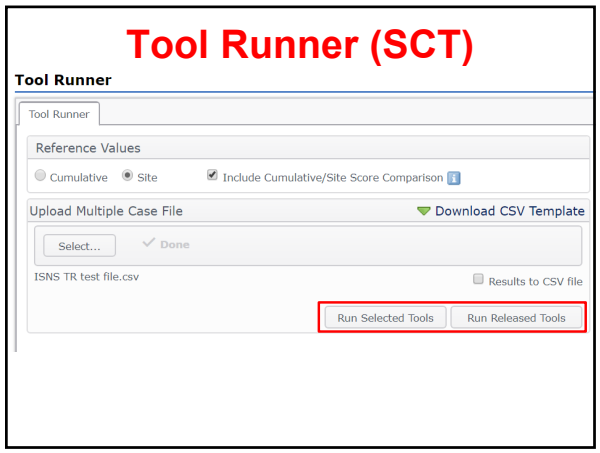
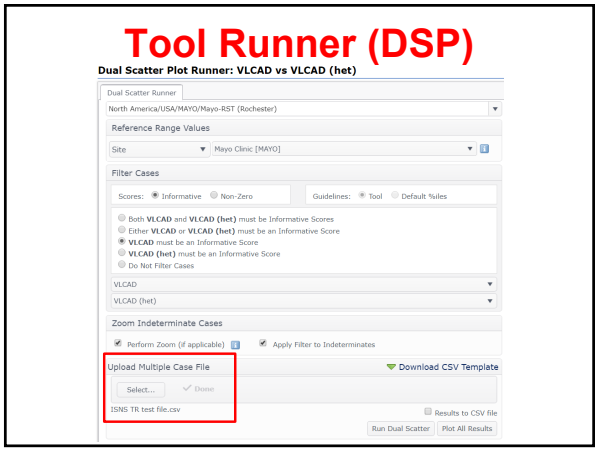


110



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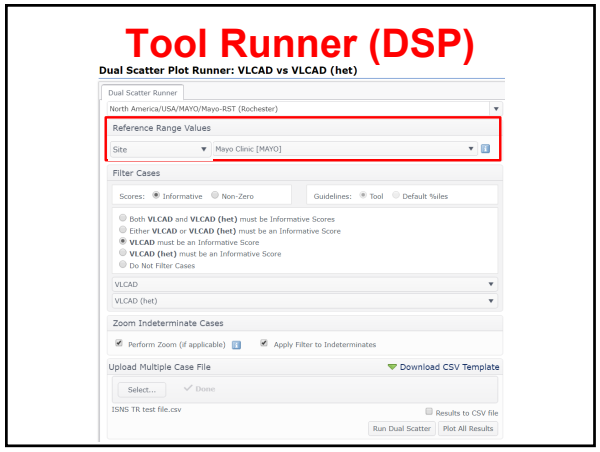
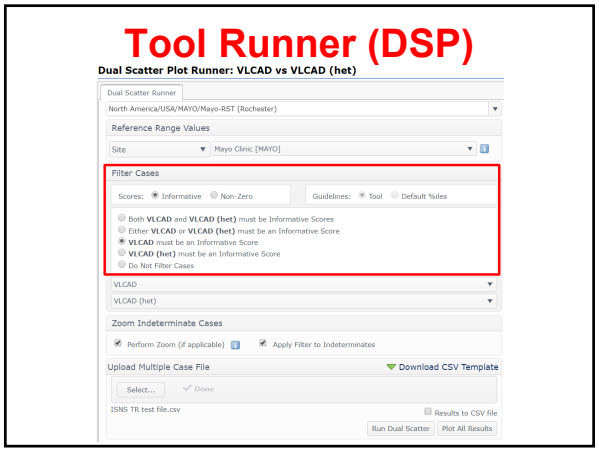


112



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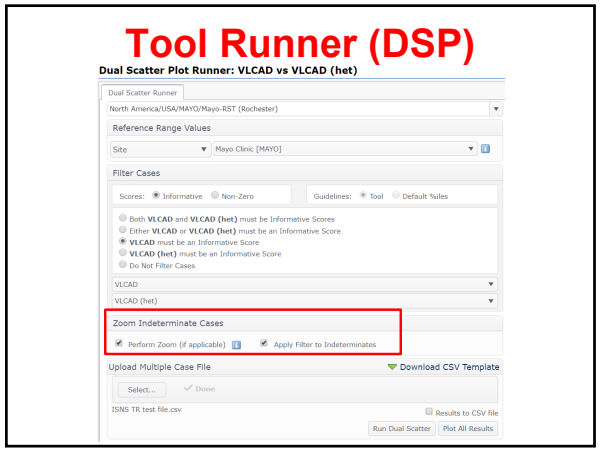
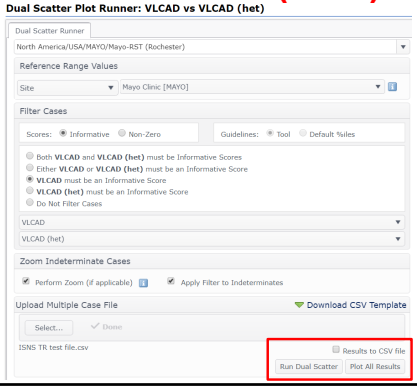


114

Tool Runner (DSP)

Dual Scatter Plot Runner: VLCAD vs VLCAD (het)



115

2nd Tier Tests


J Inherit Metab Dis
DOI 10.1007/s10545-007-0691-y
NEWBORN SCREENING

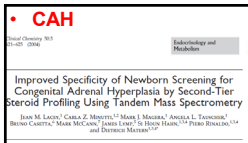
Reduction of the false-positive rate in newborn screening by implementation of MS/MS-based second-tier tests: The Mayo Clinic experience (2004–2007)

D. Matern · S. Tortorelli · D. Oglesbee · D. Gavrilov · P. Rinaldo

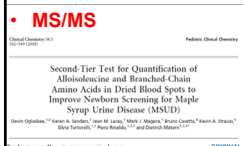
- A cost effective approach to improve specificity when reference and disease ranges overlap considerably
- Same specimen, no additional patient contact
- Normal results overrule primary screening

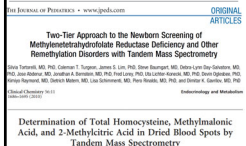
116

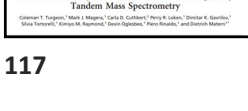
- **CAH**


Improved Specificity of Newborn Screening for Congenital Adrenal Hyperplasia by Second-Tier Steroid Profiling Using Tandem Mass Spectrometry

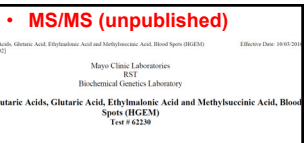
- **MS/MS**


Second-Tier Test for Quantification of Alloisoleucine and Branched-Chain Amino Acids in Dried Blood Spots to Improve Newborn Screening for Maple Syrup Urine Disease (MSUD)

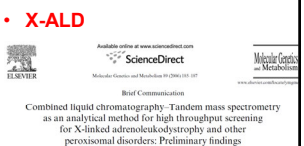

Two-Tier Approach to the Newborn Screening of Methylenetetrahydrofolate Reductase Deficiency and Other Remethylation Disorders with Tandem Mass Spectrometry


Determination of Total Homocysteine, Methylmalonic Acid, and 2-Methylcitric Acid in Dried Blood Spots by Tandem Mass Spectrometry

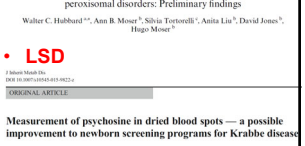
- **MS/MS (unpublished)**


Mayo Clinic Laboratories
RST
Biochemical Genetics Laboratory
Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid and Methylsuccinic Acid, Blood Spots (HGEM)
Test # 62230

- **X-ALD**

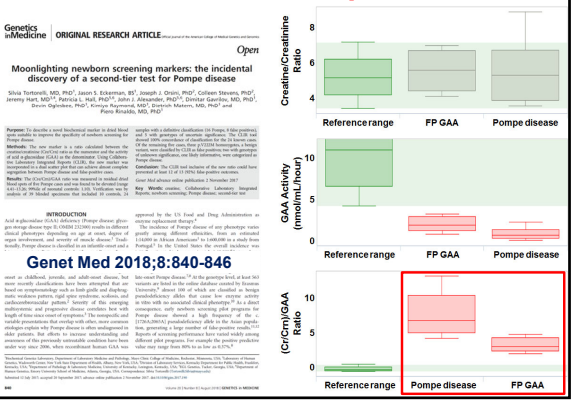

Brief Communication
Combined liquid chromatography–Tandem mass spectrometry as an analytical method for high throughput screening for X-linked adrenoleukodystrophy and other peroxisomal disorders: Preliminary findings

- **LSD**


ORIGINAL ARTICLE
Measurement of psychosine in dried blood spots — a possible improvement to newborn screening programs for Krabbe disease

117

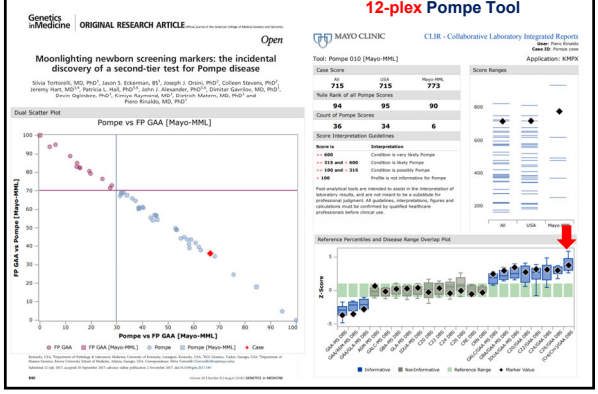
2nd Tier Test for Pompe Disease



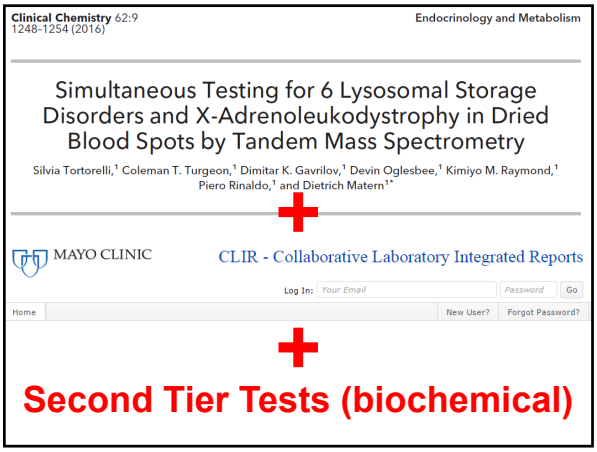
118

2nd Tier Test for Pompe Disease

12-plex Pompe Tool



119



Second Tier Tests (biochemical)

120

Clinical Chemistry 62:9
1248-1254 (2016)

Endocrinology and Metabolism

Simultaneous Testing for 6 Lysosomal Storage Disorders and X-Adrenoleukodystrophy in Dried Blood Spots by Tandem Mass Spectrometry

Silvia Tortorelli,[1] Coleman T. Turgeon,[1] Dimitar K. Gavrilov,[1] Devin Oglesbee,[1] Kimiyo M. Raymond,[1] Piero Rinaldo,[1] and Dietrich Matern[1]*

Near 0% FPR
for Pompe, MPS I, and X-ALD is achievable without additional patient contact and NO molecular testing

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Outline

- Introduction to CLIR
- Result adjustments for continuous / categorical covariates, and location
- The RUST (the RUSP post-analytical tool)
- Precision newborn screening workflow
- Example of performance (LSD, CH, CF)

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MS/MS Performance
(Interpretive Tools w/o cutoff values)

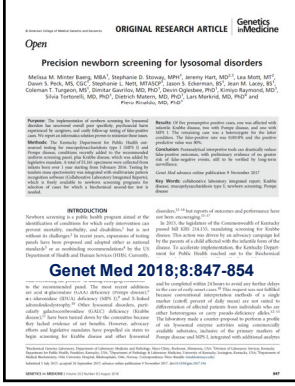
System	R4S
NBS test	MS/MS
Conditions	RUSP
From (date)	01/01/13
To (date)	12/31/13
State	MN
Newborns tested	71,207
True positive cases	38
False positive cases	17
False positive rate (FPR)	0.024%
Pos. predictive value (PPV)	67%

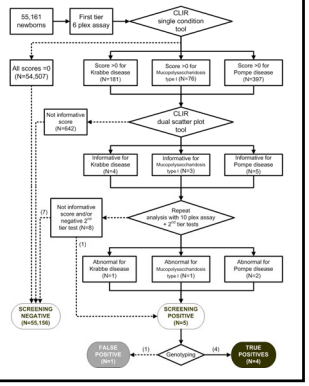

Enhanced interpretation of newborn screening results without analyte cutoff values

ORIGINAL RESEARCH ARTICLE Genetics in Medicine
Open
Postanalytical tools improve performance of newborn screening by tandem mass spectrometry

123

Precision Newborn Screening


ORIGINAL RESEARCH ARTICLE Genetics in Medicine
Open
Precision newborn screening for lysosomal disorders
Genet Med 2018;8:847-854



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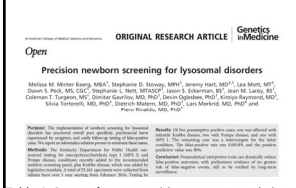
Precision Newborn Screening


ORIGINAL RESEARCH ARTICLE Genetics in Medicine
Open
Precision newborn screening for lysosomal disorders

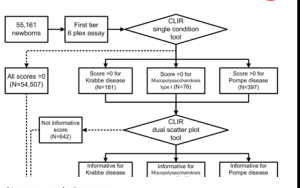


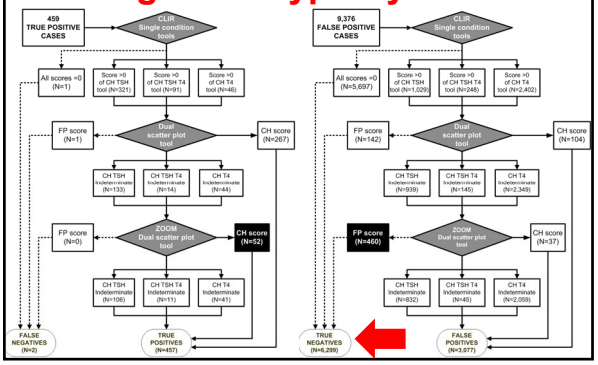
Table 1 Count of cases requiring a repeat analysis and/or second-tier tests

	Krabbe disease	MPS I	Pompe disease
Cases requiring a repeat analysis and a second-tier test[a]	11	57	15
Cases informative by repeat analysis and/or by second-tier test and reported as screen positive	1	2	2
Confirmed true positives	1	1	2
Confirmed false positives	0	1[c]	0
Detection rate	1:55,161	1:55,161	1:27,581
False-positive rate	0%	0.0018%	0%
Positive predictive value	100%	50%	100%

MPS I, mucopolysaccharidosis type I.
[c]Counts include additional cases where a noninformative resolution by the 6-plex dual scatter plot was overruled for sensitivity verification purposes

125

CLIR Workflow for Congenital Hypothyroidism



126

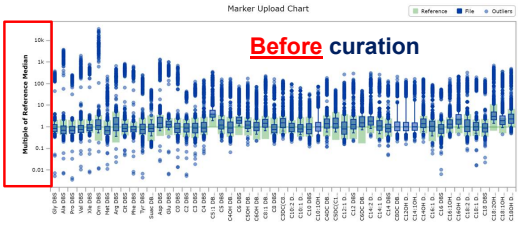
Summary and Conclusions

- It's all about the bacon (t-shirt available)

127

Summary and Conclusions

- It's all about the bacon (t-shirt available)
- Quantity (millions), quality (granularity), and curation (removal of outliers) of submitted data is an absolute necessity



128

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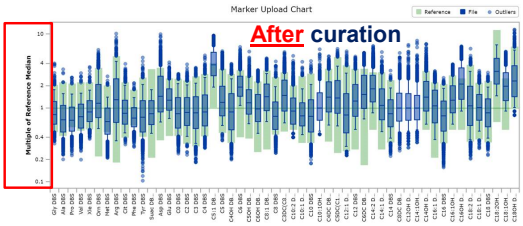

129

Summary and Conclusions

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- Quantity (millions), quality (granularity), and curation (removal of outliers) of submitted data is an absolute necessity
- Precision newborn screening is achievable rapidly by recycling data already available

130

Summary and Conclusions

- It's all about the bacon (t-shirt available)
- Quantity (millions), quality (granularity), and curation (removal of outliers) of submitted data is an absolute necessity
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- Everybody is needed, new bacon lovers are welcome (but you have to contribute data)

131

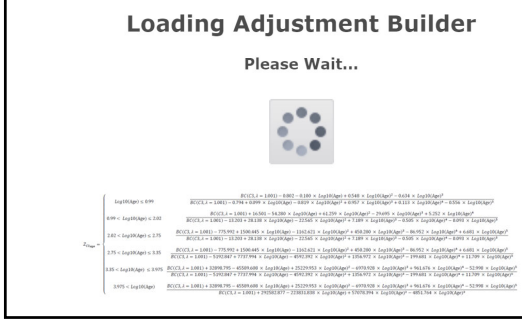
Summary and Conclusions

- It's all about the bacon (t-shirt available)
- Quantity (millions), quality (granularity), and curation (removal of outliers) of submitted data is an absolute necessity
- Precision newborn screening is achievable rapidly by recycling data already available
- Everybody is needed, new bacon lovers are welcome (but you have to contribute data)
- New releases (new tools!) of CLIR are scheduled to the end of 2019 with a special emphasis on computational performance

132

Why Computational Performance?

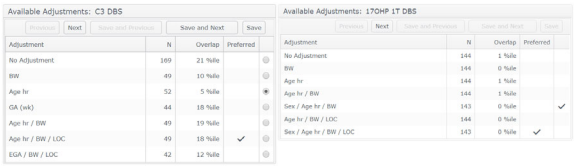
- It takes 10-20' to complete one complex adjustment



133

Why Computational Performance?

- It takes 10-20' to complete one complex adjustment
- A marker may need 5 or more adjustments to find the lowest degree of overlap to be used clinically



134

Why Computational Performance?

- It takes 10-20' to complete one complex adjustment
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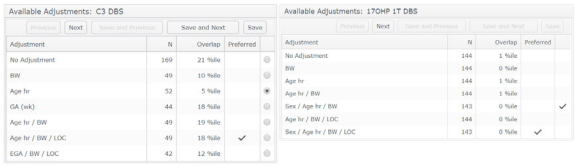
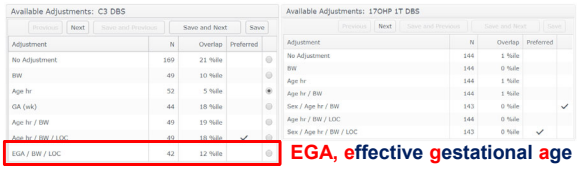
- 1-2 hours per markers, thousands of markers…..



135

Why Computational Performance?

- It takes 10-20' to complete one complex adjustment
- A marker may need 5 or more adjustments to find the lowest degree of overlap to be used clinically
- 1-2 hours per markers, thousands of markers…..
- Complex (and more time consuming) covariate EQUATIONS are being developed and tested clinically



EGA, effective gestational age

(created by Robert Currier and Lars Mørkrid)

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Global Implementation of Precision Newborn Screening

- For every current and future marker compile
  - Up to 10,000,000 ref. profiles with detailed covariates
  - or… >1,000 cases per sex per hour of life (0-1 yr)
- Generate reference moving %iles adjusted for
  - 2 continuous covariates
  - 1 categorical covariate
  - $(location)_n$

- For every target condition compile
  - >1,000 confirmed cases with detailed covariates
  - >10,000 false positive cases (10:1 ratio)
- Screening for 100+ conditions with a cumulative FPR <0.1% (<0.01% per test), sustained by 2nd tier tests

137

Global Implementation of Precision Newborn Screening

- For every current and future marker compile
  - Up to 10,000,000 ref. profiles with detailed covariates
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  - 2 con
  - 1 cat
  - (locat
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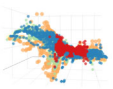
  - >10,000 false positive cases (10:1 ratio)
- Screening for 100+ conditions with a cumulative FPR <0.1% (<0.01% per test), sustained by 2nd tier tests

Precision newborn screening is NEAR ZERO false positive rate for ALL TESTS combined WORLDWIDE



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Grateful Acknowledgment of CLIR Team & External Collaborators

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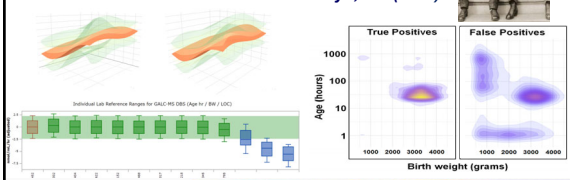
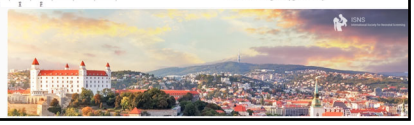
and Thank YOU for Your Attention

"Today the only thing that is permanent is change"

Charles H. Mayo, MD (1919)



11th ISNS EUROPEAN REGIONAL MEETING
Bratislava, Slovakia



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