Bringing Reference Intervals into the Era of Precision Medicine

Piero Rinaldo, MD, PhD
Professor of Laboratory Medicine
T. Denny Sanford Professor of Pediatrics
Mayo Clinic, Rochester, MN (USA)

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Association of Clinical Biochemists in Ireland
Athlone, Ireland
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Outline

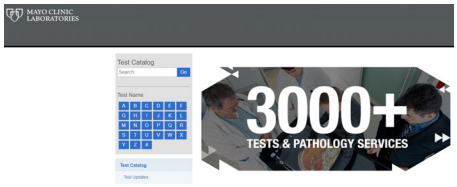
- The magnitude of the problem: Limitations of past state (partition bins, cutoff values)
- Current state: Collaborative Laboratory Integrated Reports (CLIR)
- The making of individualised reference ranges (how does it work)
- Future state: A proposal to move forward (how lab tests should be routinely ordered in the era of personalized medicine)

Outline

The magnitude of the problem: Limitations of past state (partition bins, cutoff values)

The Magnitude of the Problem

- 2,000+ Mayo lab tests with *numerical* results



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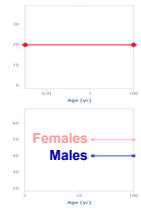
- 2,000+ Mayo lab tests with numerical results
- Virtually all of them use *arbitrary* bins & cutoffs



often NONE for pediatric patients

< or =3 months: not established

Reference values have not been established for patients who are <12 months of age

TRIGLYCERIDES

2-9 years:

Acceptable: <75 mg/dL

0-19 years: not established

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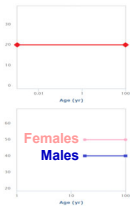

Hystorically, the clinical laboratory has FAILED to support pediatric medicine adequately

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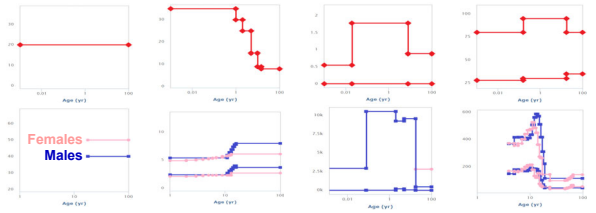

The Magnitude of the Problem

- 2,000+ Mayo lab tests with numerical results
- Virtually all of them use arbitrary bins & cutoffs
- ***Severely affected*** are multi-analyte tests that require pattern recognition of complex profiles and subjective interpretation

Amino acids	Reference Values	AGE BINS					
Plasma	Plasma Amino Acid Reference Values (nmol/mL)	Age Groups					
		<24 Months		2-17 Years		> or =18 Years	
Urine	Urine Amino Acid Reference Values (nmol/mg creatinine)	Age Groups					
		< or =12 Months	13-35 Months	3-6 Years	7-8 Years	9-17 Years	> or =18 Years

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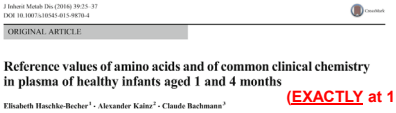
J Inherit Metab Dis (2016) 39:25–37
DOI 10.1007/s10545-015-9870-4

ORIGINAL ARTICLE

Reference values of amino acids and of common clinical chemistry in plasma of healthy infants aged 1 and 4 months

Elisabeth Haschke-Becher[1] · Alexander Kainz[2] · Claude Bachmann[3]

(EXACTLY at 1 & 4 months)

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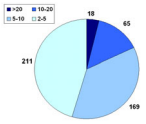
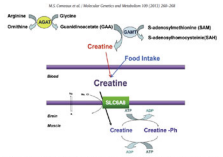
How many tests with >1 markers?



N = 463

The Urine CREATINE Panel as a Model of Past State

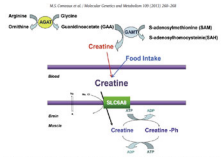


Three Marker Panel

	GAA		Creatine (Cr)		Creatinine (Crn)		Cr/Crn	
	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma
GAMT	↑	↑	↓ - N	↓	↓ - N	↓ - N	↓ - N	-
AGAT	↓ - N	↓ - N	↓ - N	↓	↓ - N	↓ - N	↓ - N	-
CRTR (♀)	N	N	N – ↑	N	↓ - N	↓ - N	N – (↑)	-
CRTR (♂)	N	N	N – ↑	N	↓ - N	↓ - N	↑	-

- Normalization for urine creatinine is not an option

The Urine CREATINE Panel as a Model of Past State



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AGAT	↓ - N	↓ - N	↓ - N	↓	↓ - N	↓ - N	↓ - N	-
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- **Normalization for urine creatinine is not an option**
- **Most common disorder (x-linked SLCA8 def.) is detectable only by a ratio (Cre/Cn)**

Test ID: CRDPU

Creatine Disorders Panel, Urine

Reference Values **(based on the analysis of ~120 samples)**

Males

Age	Creatinine (nmol/mL)	Guanidinoacetate (nmol/mL)	Creatine (nmol/mL)	Creatine/ Creatinine
< or =31 days	430-5240	9-210	12-2930	0.02-0.93
32 days-23 months	313-9040	16-860	18-10490	0.02-2.49
2-4 years	1140-12820	90-1260	200-9210	0.04-1.75
5-18 years	1190-25270	40-1190	60-9530	0.01-0.96
>18 years (male)	3854-23340	30-710	7-470	0.00-0.04

Females

Age	Creatinine (nmol/mL)	Guanidinoacetate (nmol/mL)	Creatine (nmol/mL)	Creatine/ Creatinine
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>18 years	1540-18050	30-760	5-2810	0.00-0.46

https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/88697

Limitations of Current State

- **Why were 120 samples enough?**

CLINICAL AND LABORATORY STANDARDS INSTITUTE

EP28-A3c
Vol. 28 No. 30
Formerly C28-A3c
ISBN 1-56238-682-4
ISSN 0273-3099
Vol. 28 No. 30

Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition

Volume 28 Number 30

…***the best means to establish a reference interval*** is to collect samples from a sufficient number of **qualified reference individuals** to yield **a minimum of 120 samples** for analysis, by non parametric means, for each partition (eg, sex, age range)

High/Low Cutoffs (Males) Urine Creatine

Age	Creatine (nmol/mL)
< or =31 days	12-2930
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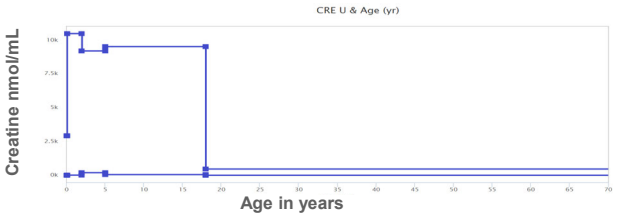
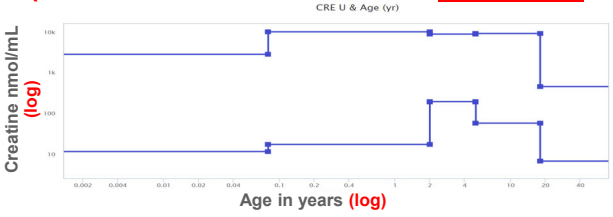
High/Low Cutoffs (Males) Urine Creatine

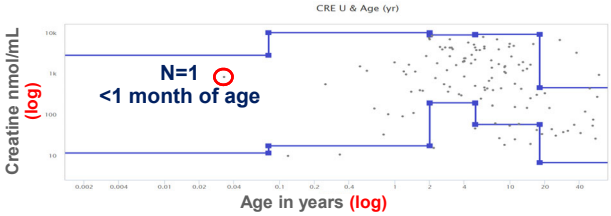


High/Low Cutoffs (Males) Urine Creatine (marker and covariate on a log scale)



Are 120 samples enough?

120 Random Male Samples (0-70 yr)



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Limitations of Current State

- **Why were 120 samples enough?**

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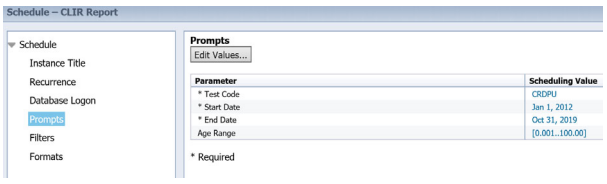
…***the best means to establish a reference interval*** is to collect samples from a sufficient number of **qualified reference individuals** to yield **a minimum of 120 samples** for analysis, by non parametric means, for each partition (eg, sex, age range)

… individual laboratories should focus more on ***verifying*** reference intervals established elsewhere, a much less formidable task.

A major advantage of this options there is no need to collect samples from reference individuals. **One can use existing samples, even from subjects not known to be healthy** ….

Retrospective Data Mining (Clinical Samples)

REFERENCE DATA PROCUREMENT → POTENTIAL SOURCES
Retrospective data mining (LIS)
Development project (new test)
External collaborators



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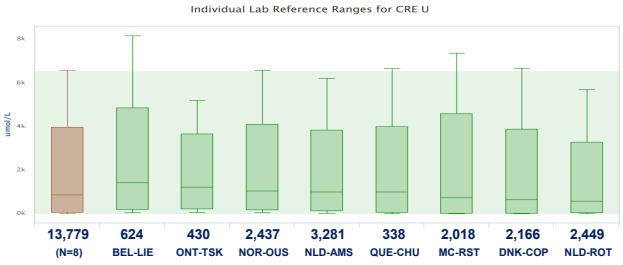
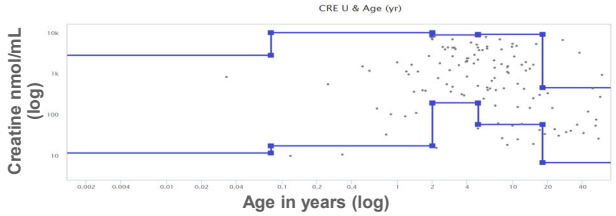
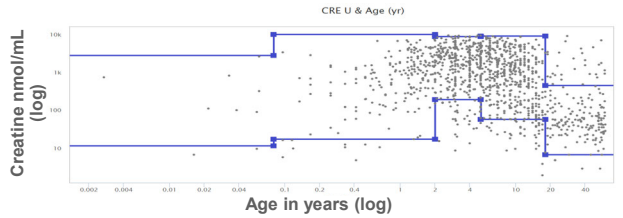


120 Random Male Samples (0-70 yr)
(Clinical Specimens Interpreted as NORMAL)



1,200 Random Male Samples (0-70 yr)
(Clinical Specimens Interpreted as NORMAL)



12,000 Random Samples (0-70 yr)
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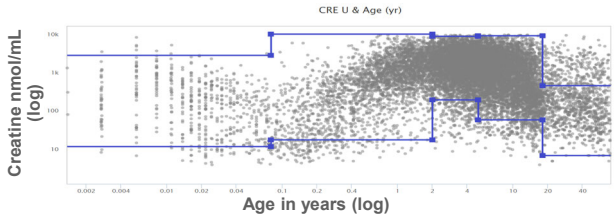
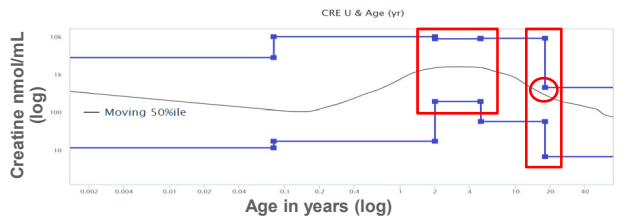
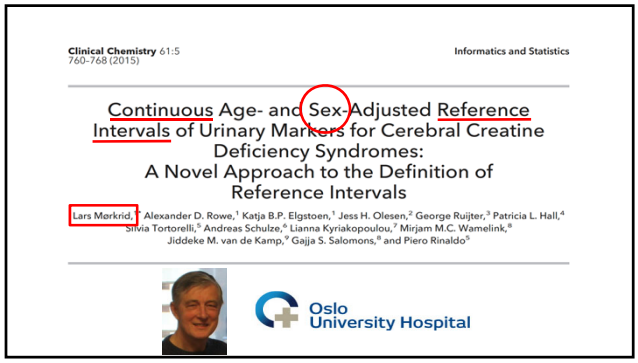


High/Low Cutoffs (Males) Urine Creatine Moving Median (N=13,779) *vs.* Cutoffs





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

Test ID: CRDPU

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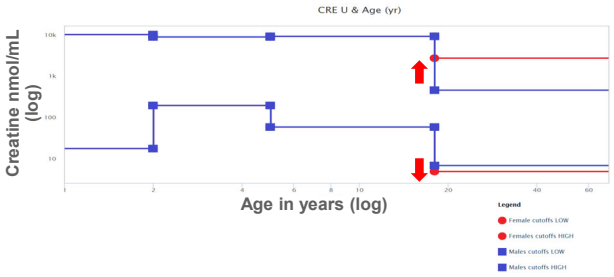
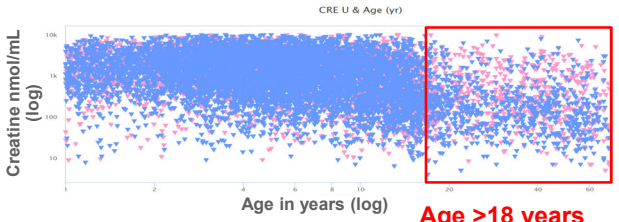


Males *vs.* Females Urine Creatine



Is there a better, simple (automated), and OBJECTIVE way to tell if there is a significant M/F difference?

Age >18 years

Female n=559

Male n=743

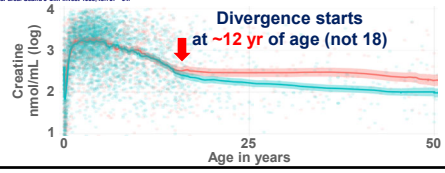
The Gowans' Plot

Gowans' Plot

Gowans EM, Pedersen PH, Blaaberg O, Herder 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 ± 1/8 SD
vs.
Female median ± 1/8 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



Divergence starts at ~12 yr of age (not 18)

Can we MERGE M/F data?

Outline

- **The magnitude of the problem: Limitations of past state (partition bins, cutoff values)**
- **Current state: Collaborative Laboratory Integrated Reports (CLIR)**

CLIR™
collaborative laboratory integrated reports

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**

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- Since 2012, CLIR is supported by institutional funding and has been approved as an official product of Mayo Clinic

MAYO CLINIC

CLIR - Collaborative Laboratory Integrated Reports

https://clir.mayo.edu

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- (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

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

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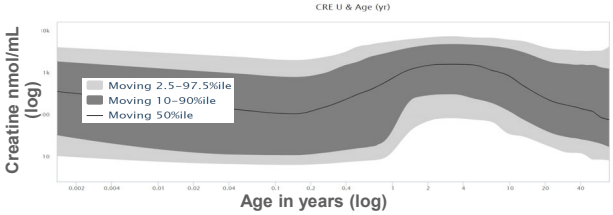
What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous (moving) covariate-adjusted percentiles
- Enhances the clinical utility of individual markers
- Replaces analyte cutoff values
- Replaces diagnostic sequential algorithms (“and”)

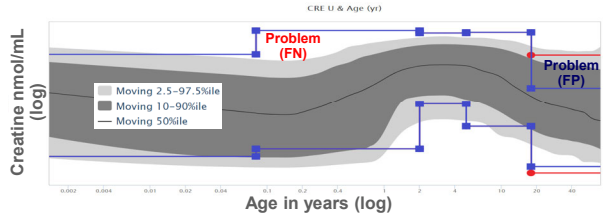
Continuous Moving Percentiles Urine Creatine (Unadjusted)



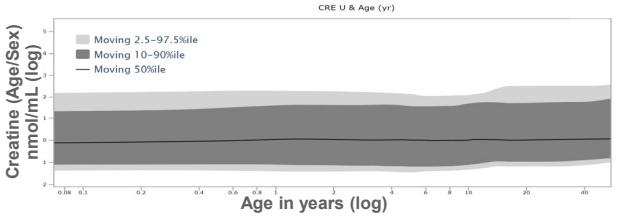
Continuous Moving Percentiles Urine Creatine (Unadjusted)

a.k.a. the “Bacon Plot”

Continuous Moving Percentiles Urine Creatine (Unadjusted)

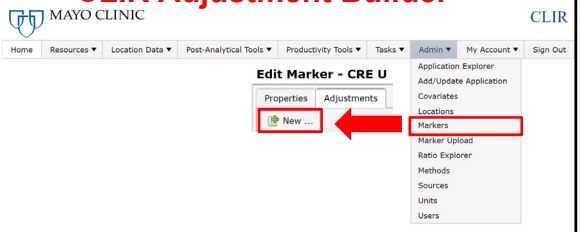


Continuous Moving Percentiles Urine Creatine (ADJUSTED)



How is this done?

CLIR Adjustment Builder



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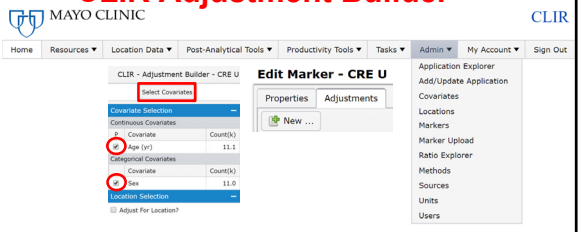

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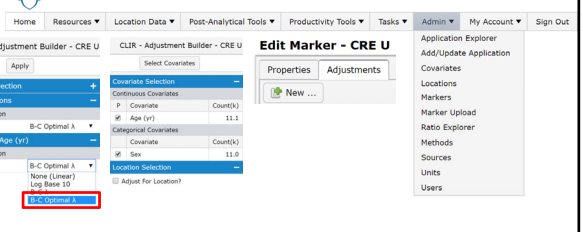
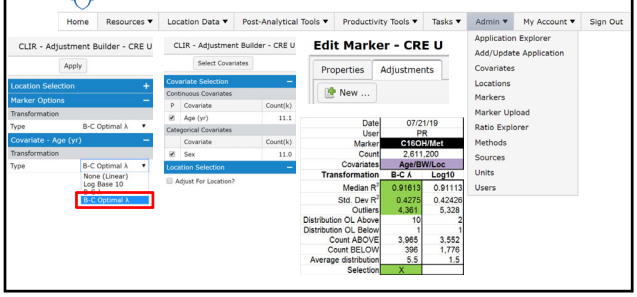
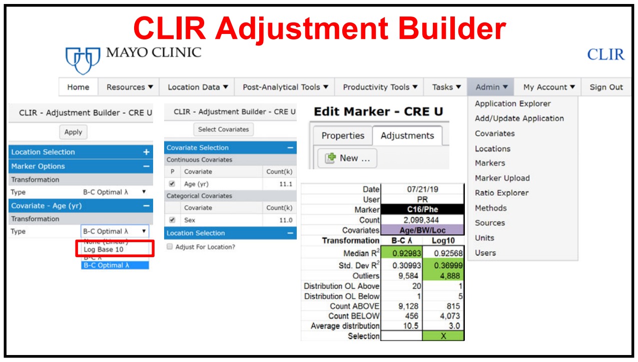
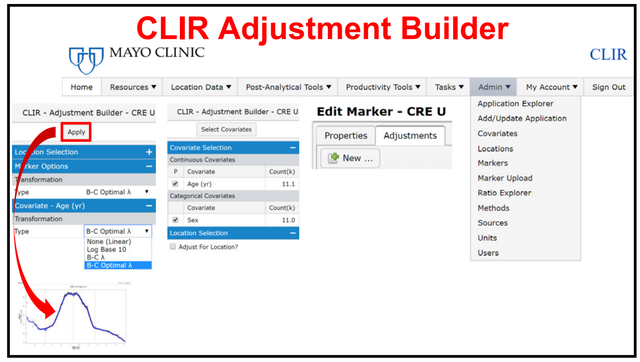
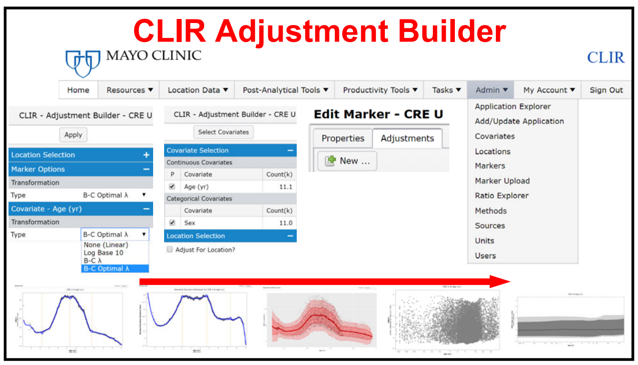


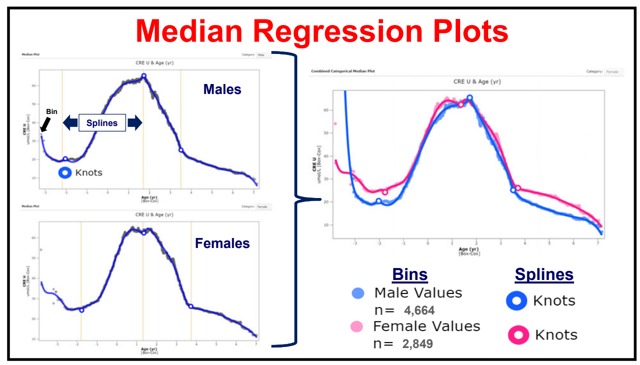
CLIR Adjustment Builder

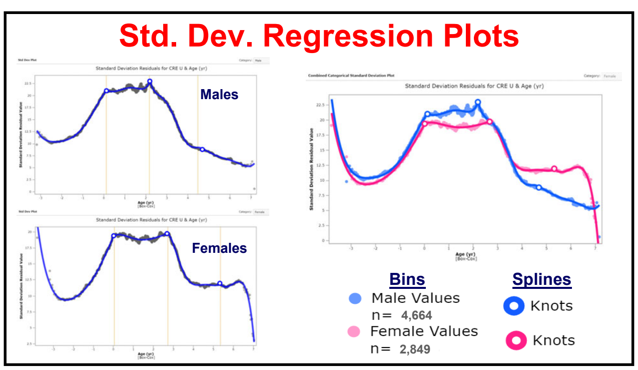


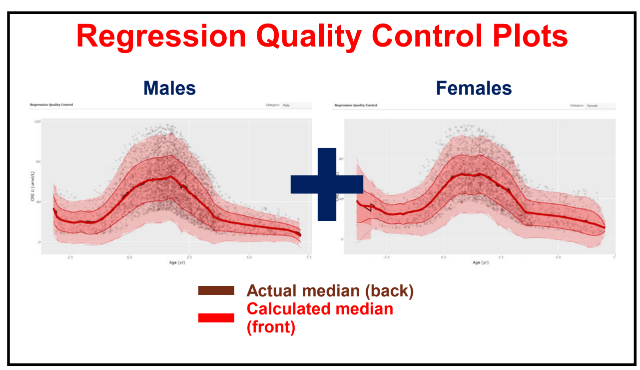

CLIR Adjustment Builder
MAYO CLINIC
CLIR
Home
Resources
Location Data
Post-Analytical Tools
Productivity Tools
Tasks
Admin
My Account
Sign Out
Edit Marker - CRE U
Properties
Adjustments
New ...
Application Explorer
Add/Update Application
Covariates
Locations
Markers
Marker Upload
Ratio Explorer
Methods
Sources
Units
Users


CLIR Adjustment Builder
MAYO CLINIC
CLIR
Apply
Edit Marker - CRE U
Properties
Adjustments
New ...


CLIR Adjustment Builder
MAYO CLINIC
CLIR
Edit Marker - CRE U
Properties
Adjustments
New ...

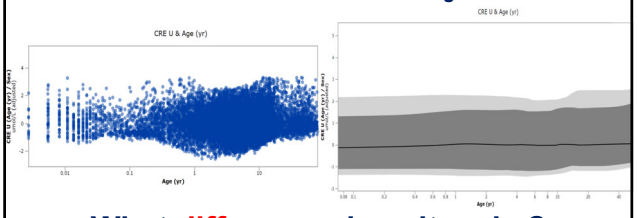

Median Regression Plots
Males
Bin
Splines
Knots
Females
Bins
Male Values
n= 4,664
Female Values
n= 2,849
Splines
Knots
Knots


Std. Dev. Regression Plots
Males
Females
Bins
Male Values
n= 4,664
Female Values
n= 2,849
Splines
Knots
Knots


Regression Quality Control Plots
Males
Females
Actual median (back)
Calculated median
(front)

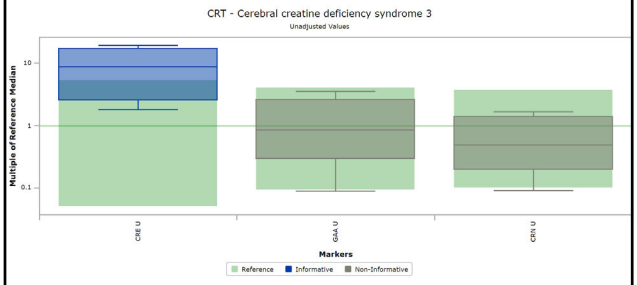
Adjusted Marker vs Covariate Plot

Individual Values | **Moving Percentiles**

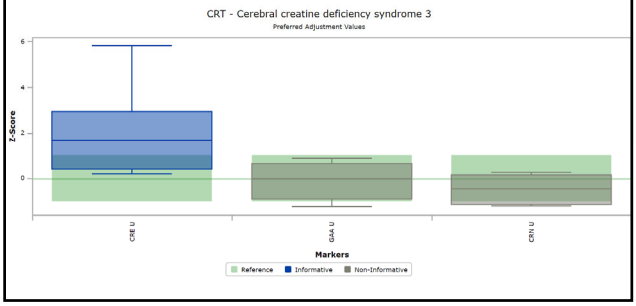


What difference does it make?

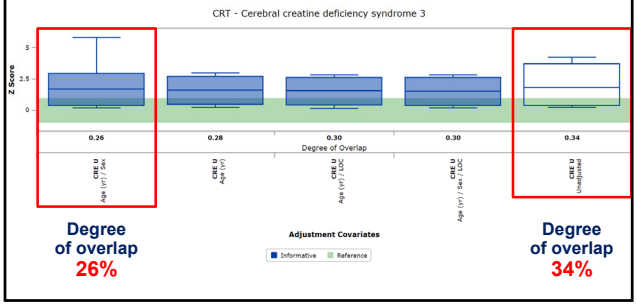
Unadjusted Plot by Condition



Adjusted Plot by Condition



Adjustment Comparison Plot



Degree of overlap 26%

Degree of overlap 34%

Beyond ONE Continuous Covariate

IRT (Cystic Fibrosis)

Covariate Selection

Continuous Covariates

P	S	Covariate	Count(k)
☑	☐	Age hr	2,827.9
☐	☑	BW	2,820.9
☐	☐	EGA	1,870.8
☐	☐	GA (wk)	1,871.1

Categorical Covariates

	Covariate	Count(k)
☐	Sex	2,815.3

Location Selection

☑ Adjust For Location?

CLIR - Adjustment Builder

Select Covariates

CLIR can create simultaneous adjustments for 2 continuous 1 categorical covariates & locations (n)

17OHP (CAH)

Covariate Selection

Continuous Covariates

P	S	Covariate	Count(k)
☑	☐	Age hr	3,166.8
☐	☑	BW	3,159.5
☐	☐	EGA	1,955.2
☐	☐	GA (wk)	1,955.5

Categorical Covariates

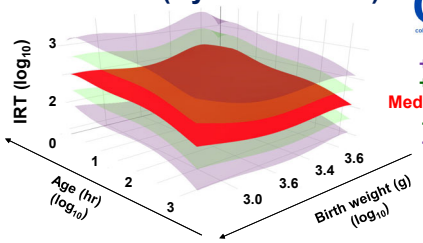
	Covariate	Count(k)
☑	Sex	2,901.9

Location Selection

☑ Adjust For Location?

Continuous Moving Reference Ranges Adjusted for AGE & BW & Location

IRT (Cystic Fibrosis)



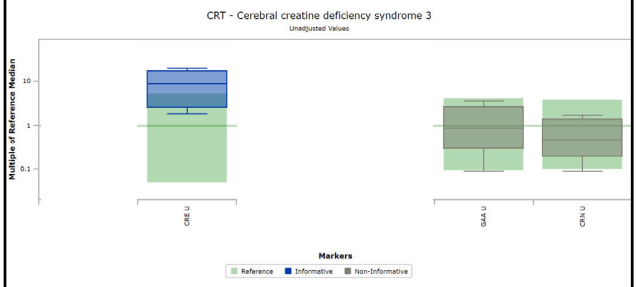
CLiR™ collaborative laboratory integrated reports

+ 2SD
+ 1SD
Median plane
- 1SD
- 2SD

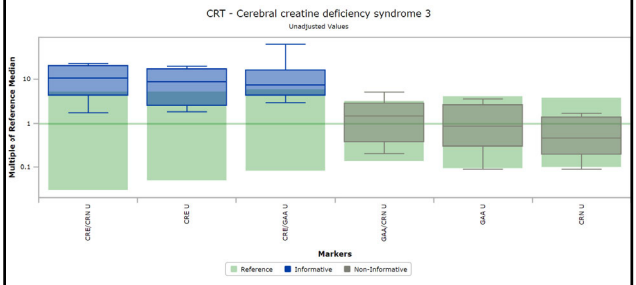
What Does CLIR DO, Exactly?

- Replaces conventional reference ranges
  - With continuous (moving) covariate-adjusted percentiles
- Enhances the clinical utility of individual markers
  - With all possible permutation of calculated ratios
- Replaces analyte cutoff values
  - With an integrated scoring based on the degree of overlap between reference ranges and condition-specific disease ranges, all adjusted for relevant covariates
- Replaces diagnostic sequential algorithms ("and")

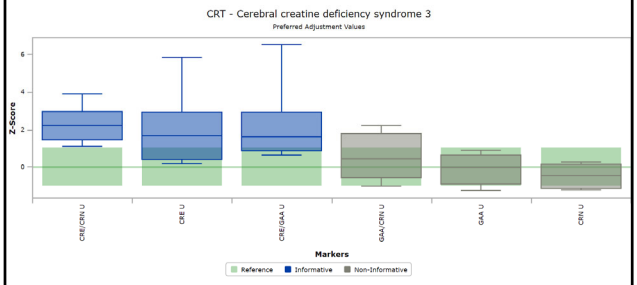
Unadjusted Plot by Condition



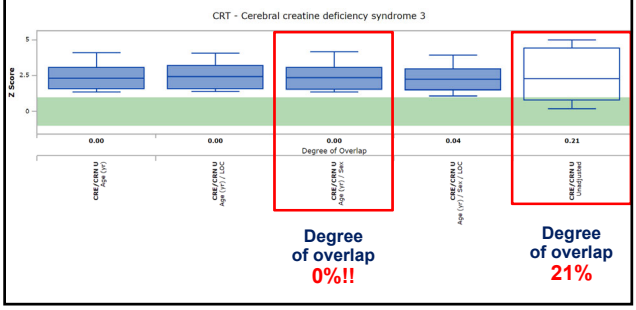
Unadjusted Plot by Condition



Adjusted Plot by Condition



Adjustment Comparison Plot

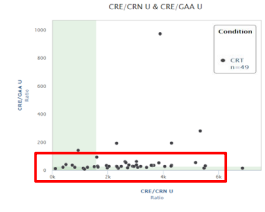


Degree of overlap 0%!!

Degree of overlap 21%

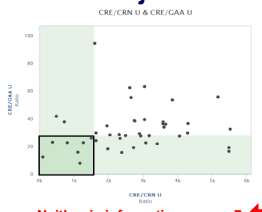
The Clinical Utility of COMBINING Covariate-Adjusted Ratios

Unadjusted



The Clinical Utility of COMBINING Covariate-Adjusted Ratios

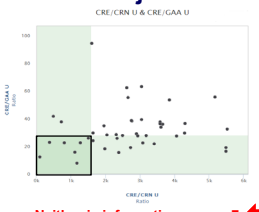
Unadjusted



Neither is informative	7
Only one informative	13
Both are informative	29

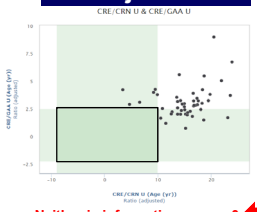
The Clinical Utility of COMBINING Covariate-Adjusted Ratios

Unadjusted



Neither is informative	7
Only one informative	13
Both are informative	29

Adjusted



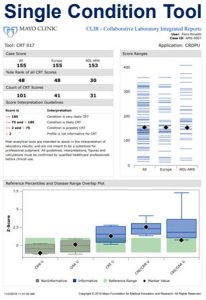
Neither is informative	0
Only one informative	21
Both are informative	28

What Does CLIR DO, Exactly?

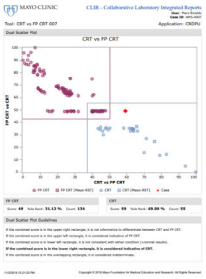
- Replaces conventional reference ranges
  - With continuous (moving) covariate-adjusted percentiles
- Enhances the clinical utility of individual markers
  - With all possible permutation of calculated ratios
- Replaces analyte cutoff values
  - With an integrated scoring based on the degree of overlap between reference ranges and condition-specific disease ranges, all adjusted for relevant covariates
- Replaces diagnostic sequential algorithms ("and")
  - With tool-based post-analytical parallel algorithms ("or")

Post-Analytical Interpretive Tools

Single Condition Tool



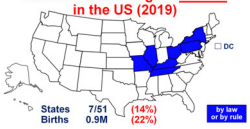
Dual Scatter Plot



Krabbe Disease

- Defect
  - Lysosomal galactocerebrosidase (GALC)
- Incidence (infantile form)
  - 1:~400,000 (infantile onset)
- Timing of clinical onset
  - First year of life
- Severity of disease
  - Irritability, feeding difficulties, progressive spasticity, blindness and deafness, loss of voluntary movements, death occurs in infancy or childhood
- Treatment
  - Human stem cell transplantation (HSCT)

Newborn Screening for Krabbe in the US (2019)



NBS for Krabbe (without CLIR)

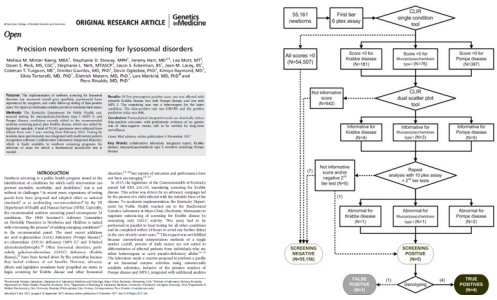
ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Newborn screening for Krabbe disease in New York State: the first eight years' experience

Joseph J. Orsini, PhD[1], Denise M. Kay, PhD[1], Carlos A. Saavedra-Matiz, MD[1], David A. Wenger, PhD[2], Patricia K. Duffner, MD[3], Richard W. Erbe, MD[4], Chad Biski, BS[1], Monica Martin, BS[1], Lea M. Krein, BS[1], Matthew Nichols, BS[1], Joanne Kurtzberg, MD[5], Maria L. Escolar, MD[6], Darius J. Adams, MD[7,8], Georgianne L. Arnold, MD[8,9], Alejandro Iglesias, MD[10], Patricia Galvin-Parton, MD[11], David F. Kronn, MD[12], Jennifer M. Kwon, MD[9], Paul A. Levy, MD[13], Joan E. Pellegrino, MD[14], Natasha Shur, MD[7], Melissa P. Wasserstein, MD[15], Michele Caggana, ScD, FACMG[1] and the New York State Krabbe Disease Consortium

Conclusions: The positive predictive value of KD screening in NYS is 1.4% (5/346) considering confirmed infantile cases. The incidence of infantile KD in NYS is approximately 1 in 394,000, but it may be higher for later-onset forms.

NBS for Krabbe (with CLIR)


ORIGINAL RESEARCH ARTICLE | Genetics in Medicine

Open

Precision newborn screening for lysosomal disorders

NBS for Krabbe (with CLIR)

Year	2016	2017	2018	2019	ALL
Volume (KY)	48,125	55,453	55,152	42,956	201,686
Abnormal (CLIR)	13	9	5	18	45 (0.02%)
*Normal 2TT	12/13	9/9	5/5	18/18	44/45
Reported positive	1	0	0	0	1
Confirmed TP	1	0	0	0	0
Confirmed FP	0	0	0	0	0
Detection rate	1:55,151	n/a	n/a	n/a	1:201,686
* h-PSY 30kb del <1.5 -/- FPR	0%	0%	0%	0%	0%
PPV	100%	n/a	n/a	n/a	100%

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,*]

MAYO CLINIC

CLIR - Collaborative Laboratory Integrated Reports

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Second Tier Tests (biochemical)

Clinical Chemistry 62:9
1248-1254 (2016)

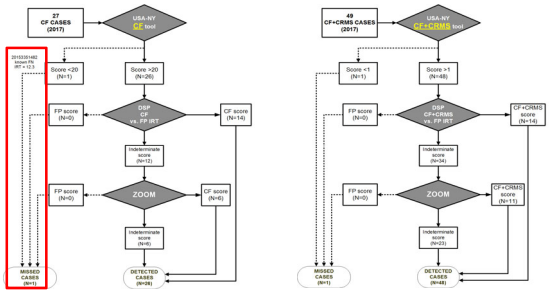
Endocrinology and Metabolism

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

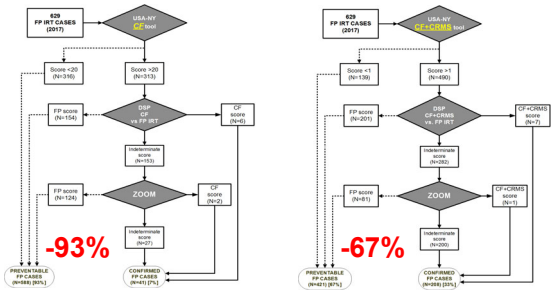
Near 0% FPR
for Pompe, MPS I, X-ALD and KRABBE is achievable without additional patient contact and NO molecular testing

Second Tier Tests (biochemical)

Outcome of NYS CF+CRMS Cases (N=49)

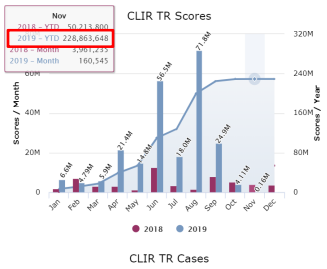


Outcome of NYS FP IRT Cases (N=629)



Post-Analytical Interpretive Tools 2019 Utilization (YTD)

~750K/day



CLIR TR Cases

Outline

- The magnitude of the problem: Limitations of past state (partition bins, cutoff values)
- Current state: Collaborative Laboratory Integrated Reports (CLIR)
- The making of individualized reference ranges (how does it work)

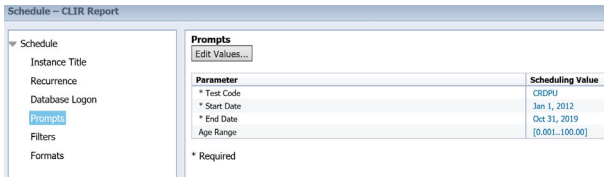
Images shown in the next slides are from different CLIR applications for the following tests:

- CRDPU, total serum Calcium (CA), s-TSH, Hb (CBC)

How to Retrospectively Make Individualized Reference Ranges from Clinical Testing Results

- Data mining from LIS (SCC Soft since 11/2011)
- Removal of obvious outliers (± 10% highest/lowest cutoff)
- Data sorting (site, sex, age)
- Filtering by age- and sex-specific peripheral percentiles
- CLIR productivity tools
  - Validation tool (gateway of data uploads)
  - Reference ranges by covariate
  - Reference data review (manual removal of residual outliers)

Data Mining from LIS



Removal of Gross Outliers

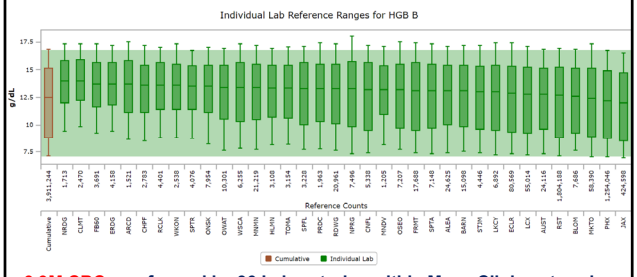
Test ID: CA
Calcium, Total, Serum

- **Values removed (± 10%)**
  - **>12.1 mg/dL**
  - **< 7.4 mg/dL**

Reference Values

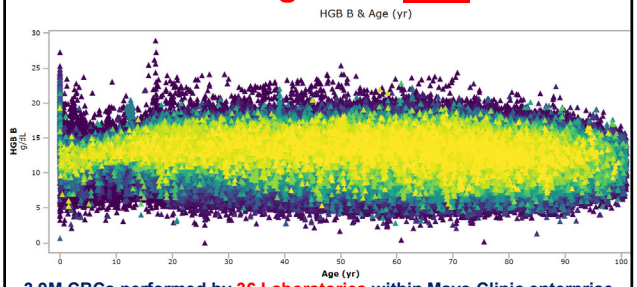
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

Data Sorting - Site



3.9M CBCs performed by 36 Laboratories within Mayo Clinic enterprise

Data Sorting - Site Age

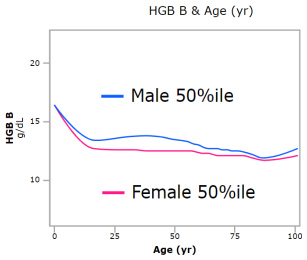


3.9M CBCs performed by 36 Laboratories within Mayo Clinic enterprise

Data Sorting - Site Age Sex

Categorical Covariates

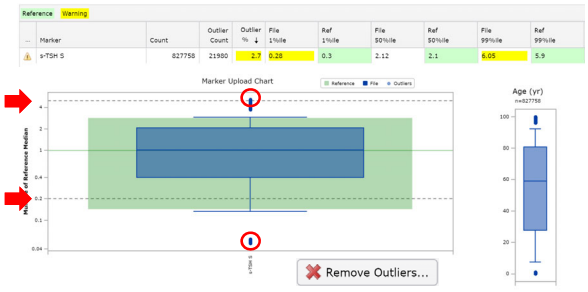
	Answer	Count
Covariate: Sex		
☐	Female	1,923,650
☐	Male	1,987,594
		3,911,244



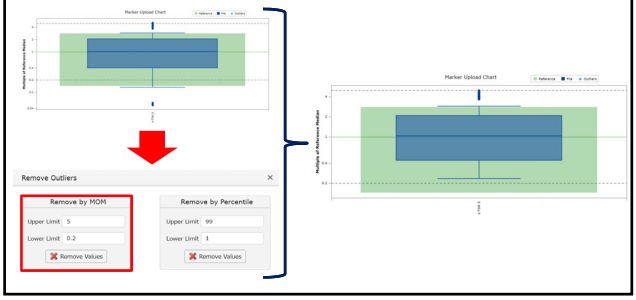
Filtering by Peripheral Percentiles

951853	Count	1375	368	228	178	181	540	962	767	606	555
Min/Max	Percentile	0.1	0.2	0.3	0.4	0.5	1	2	3	4	5
6.30/8.00	☐ 1%	6.30	6.97	6.80	7.40	7.58	6.90	7.36	7.73	7.61	7.90
7.30/8.50	☑ 5%	7.30	8.20	8.20	8.00	8.20	8.30	8.11	8.40	8.10	8.40
7.80/8.80	☐ 10%	7.80	8.60	8.80	8.60	8.60	8.70	8.50	8.60	8.30	8.60
8.90/10.10	☐ 50%	**9.30**	**9.70**	**9.90**	**10.00**	**10.10**	**9.90**	**9.60**	**9.50**	**9.40**	**9.50**
9.50/11.80	☐ 90%	10.50	10.50	10.80	11.10	11.80	11.00	10.40	10.40	10.10	10.16
9.60/12.33	☑ 95%	10.83	10.80	11.10	12.33	12.30	11.40	10.60	10.80	10.30	10.30
9.90/15.05	☐ 99%	11.80	11.30	11.55	15.05	12.86	12.56	11.72	11.43	10.60	10.70
	MAX	18.80	11.60	12.60	18.40	13.50	13.20	21.00	13.50	11.70	13.30
START	MIN	5.80	6.20	5.70	5.30	5.40	6.20	4.90	6.60	7.10	6.40

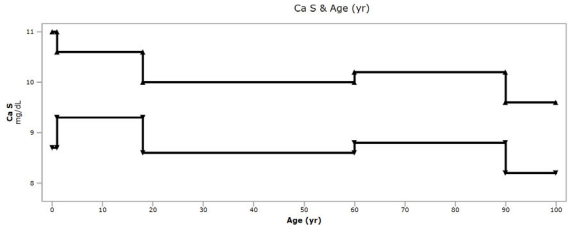
CLIR Validation Tool



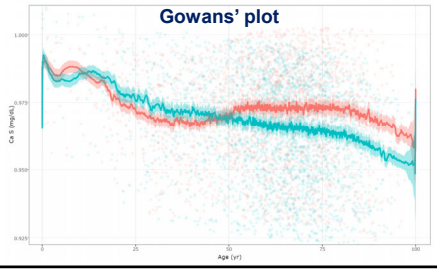
CLIR Validation Tool



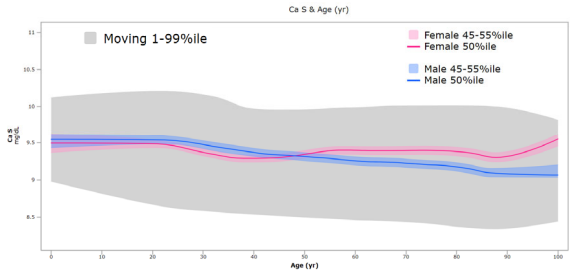
Total Calcium Reference Values (Sex Differences?)



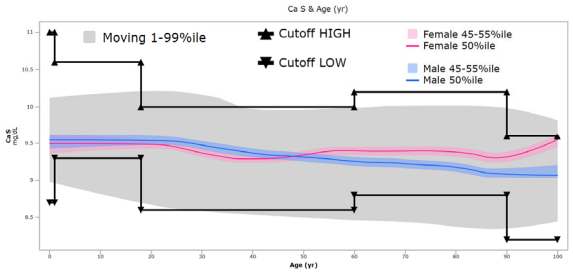
Total Calcium Reference Values (Sex Differences?) YES!



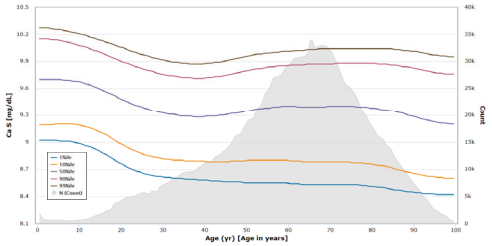
Total Calcium in Serum
Central Dispersion & Cumulative Percentiles



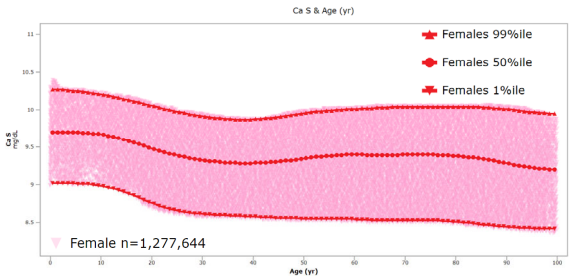
Total Calcium in Serum
Central Dispersion, Percentiles, and Cutoffs



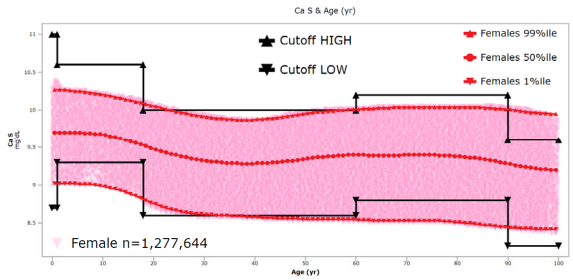
Reference Range by Covariate
FEMALE Moving Percentiles



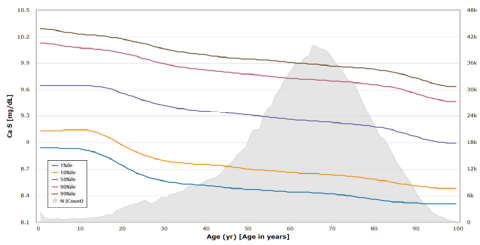
Total Calcium in Serum
FEMALE Moving Percentiles



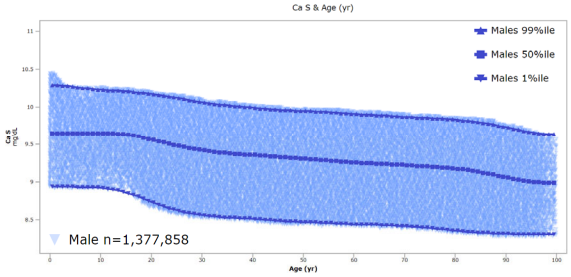
Total Calcium in Serum
FEMALE Moving Percentiles & Cutoffs



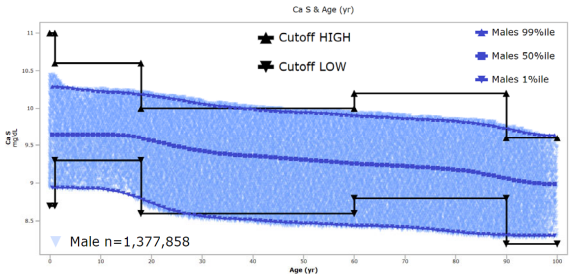
Reference Range by Covariate
MALE Moving Percentiles



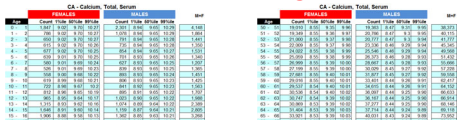
Total Calcium in Serum
MALE Moving Percentiles



Total Calcium in Serum
MALE Moving Percentiles & Cutoffs



Personalized Reference Ranges (N=2,655,502)



Personalized Reference Ranges (N=2,655,502)

Can this model be implemented in clinical practice?

Test ID: HIAA

We just did it!

5-Hydroxyindoleacetic Acid, 24 Hour, Urine

Reference Values

5HIAA, mg/24 hour

99th Percentile Cutoff

Age	Female	Male	Age	Female	Male	Age	Female	Male	Age	Female	Male	Age	Female	Male
< or <23 months	< or =2.7	< or =2.3	21 years	< or =6.2	< or =6.9	41 years	< or =7.1	< or =8.3	61 years	< or =8.3	< or =9.9	81 years	< or =8.7	< or =9.9
24-35 months	< or =3.0	< or =2.6	22 years	< or =6.2	< or =7.0	42 years	< or =7.2	< or =8.4	62 years	< or =8.4	< or =9.9	82 years	< or =8.7	< or =9.9
3 years	< or =3.2	< or =2.9	23 years	< or =6.2	< or =7.0	43 years	< or =7.3	< or =8.5	63 years	< or =8.4	< or =10.0	83 years	< or =8.7	< or =9.9
4 years	< or =3.4	< or =3.2	24 years	< or =6.3	< or =7.1	44 years	< or =7.4	< or =8.6	64 years	< or =8.4	< or =10.0	84 years	< or =8.7	< or =9.9
5 years	< or =3.6	< or =3.6	25 years	< or =6.3	< or =7.2	45 years	< or =7.4	< or =8.7	65 years	< or =8.4	< or =10.0	85 years	< or =8.6	< or =9.8
6 years	< or =3.8	< or =3.9	26 years	< or =6.3	< or =7.2	46 years	< or =7.5	< or =8.8	66 years	< or =8.5	< or =10.1	86 years	< or =8.5	< or =9.8
7 years	< or =4.0	< or =4.2	27 years	< or =6.4	< or =7.3	47 years	< or =7.6	< or =8.9	67 years	< or =8.5	< or =10.1	87 years	< or =8.4	< or =9.7
8 years	< or =4.2	< or =4.5	28 years	< or =6.5	< or =7.4	48 years	< or =7.6	< or =9.0	68 years	< or =8.5	< or =10.1	88 years	< or =8.3	< or =9.6
9 years	< or =4.5	< or =4.8	29 years	< or =6.5	< or =7.5	49 years	< or =7.7	< or =9.1	69 years	< or =8.5	< or =10.2	89 years	< or =8.1	< or =9.5
10 years	< or =4.7	< or =5.1	30 years	< or =6.6	< or =7.5	50 years	< or =7.7	< or =9.2	70 years	< or =8.5	< or =10.2	90 years	< or =7.9	< or =9.4
11 years	< or =4.9	< or =5.3	31 years	< or =6.6	< or =7.6	51 years	< or =7.8	< or =9.3	71 years	< or =8.6	< or =10.2	91 years	< or =7.6	< or =9.2
12 years	< or =5.2	< or =5.6	32 years	< or =6.7	< or =7.7	52 years	< or =7.8	< or =9.4	72 years	< or =8.6	< or =10.2	92 years	< or =7.4	< or =9.0
13 years	< or =5.4	< or =5.8	33 years	< or =6.8	< or =7.7	53 years	< or =7.9	< or =9.5	73 years	< or =8.5	< or =10.1	93 years	< or =7.1	< or =8.8
14 years	< or =5.6	< or =6.1	34 years	< or =6.8	< or =7.8	54 years	< or =8.0	< or =9.6	74 years	< or =8.5	< or =10.1	94 years	< or =7.0	< or =8.7
15 years	< or =5.7	< or =6.3	35 years	< or =6.9	< or =7.9	55 years	< or =8.1	< or =9.7	75 years	< or =8.6	< or =10.1	> 95 years	< or =6.9	< or =8.6
16 years	< or =5.9	< or =6.4	36 years	< or =6.9	< or =7.9	56 years	< or =8.1	< or =9.7	76 years	< or =8.6	< or =10.0			
17 years	< or =6.0	< or =6.6	37 years	< or =7.0	< or =8.0	57 years	< or =8.2	< or =9.8	77 years	< or =8.6	< or =10.0			
18 years	< or =6.0	< or =6.7	38 years	< or =7.0	< or =8.1	58 years	< or =8.3	< or =9.8	78 years	< or =8.6	< or =10.0			
19 years	< or =6.1	< or =6.8	39 years	< or =7.0	< or =8.2	59 years	< or =8.3	< or =9.8	79 years	< or =8.6	< or =10.0			
20 years	< or =6.1	< or =6.9	40 years	< or =7.1	< or =8.2	60 years	< or =8.3	< or =9.9	80 years	< or =8.7	< or =9.9			

Previous cutoff: <8 mg/24 h (all ages, no sex differences)

Outline

- The magnitude of the problem: Limitations of past state (partition bins, cutoff values)
- Current state: Collaborative Laboratory Integrated Reports (CLIR)
- The making of individualised reference ranges (how does it work)
- Future state: A proposal to move forward (how lab tests should be routinely ordered in the era of personalized medicine)

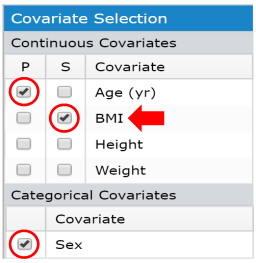
Future State: A Proposal

- The ordering of every laboratory test will include
  - Sex
  - PRECISE Age (my age *today* is 62.739726 yr)
  - HEIGHT and WEIGHT
  - Reason for referral (dream on….)

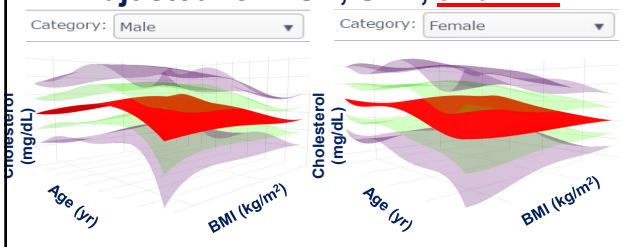
Future State: A Proposal

- The ordering of every laboratory test will include
  - Sex
  - PRECISE Age (my age *today* is 62.739726 yr)
  - HEIGHT and WEIGHT
  - Reason for referral (dream on….)
- The reporting of every laboratory test will include
  - Age, sex, and BMI adjusted reference ranges

CLIR Adjustment Builder (Covariates: AGE,SEX, and BMI)



Serum Cholesterol Ref. Range Adjusted for AGE, SEX, and BMI



Data sample from NHANES - CDC (N=15,188)

The Goal of Future State: Clinical Utility

(why we do what we do….. Agree?)

- It is critical to understand that, after all, even "perfect" reference intervals are not what is really needed in clinical practice, unless the given task, and clinical expectation, is to accurately "diagnose" healthy people!
- Comparison of results to DISEASE RANGES is far more important to answer the question whether a "non-normal" result is actually consistent with a particular disease status (from normal/abnormal to likelihood of disease)

Thank You for Your Attention

"Today the only thing
that is permanent is change"

Charles H. Mayo, MD (1919)