Harmonizing Reference Intervals (hRIs) ≠ Result Uncertainty (RU)

What do you think the main concerns will be for harmonized reference intervals in your lab?

How can we do a better job of conveying what a significant change is for a test?

Please jot down your current thoughts on these questions!

Harmonizing Reference Intervals ± Result Uncertainty

2017 OAP Annual Meeting
Deerhurst Skyline Resort,
Huntsville, Ontario
September 15, 2017

Christine Collier, PhD, FCACB
Queen's University

Learning objectives

After participating in this session, participants will be able to:

Implement pediatric hRIs in their own laboratories, and then…

Consider the use of adult hRIs, by…

Critically appraising the validity of current RIs, and then…

Developing ancillary result interpretation information, to…

Address both the MU of an analytical result, and the…

Expected RU of a patient result based on BV.

hRIs = harmonized (or common) reference intervals
MU = measurement uncertainty; RU = result uncertainty
BV = biological variation

International Initiatives - Links

- IFCC (International Federation for Clinical Chemistry)

  http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-ridl/

  Harmonization of Clinical Laboratory Test Results. eJIFCC 27(1) Feb 2016
  http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/ejifcc-(journal)/e-journal-volumes/ejifcc2016vol27/ejifcc-vol-27-no-1/
- AACC (American Association for Clinical Chemistry)

  International Harmonization Consortium

  http://www.harmonization.net/

  AACC *White Paper*: The Need to Harmonize Clinical Laboratory Test Results. 2015 July.
- AACB (Australasian Association of Clinical Biochemstry)

  http://www.rcpa.edu.au/getattachment/c268316f-dc7b-453d-8cdb-f39cf06a2f92/APUTS-Harmonised-Reference-Intervals-Chemical-Path.aspx

  JOURNAL: The Clinical Biochemist Reviews 35(4), 2014
- ACB (Association of Clinical Biochemistry in the UK)

  http://www.pathologyharmony.co.uk/
- EFLM Pre-analytical Testing Working Group (European)
  https://www.eflm.eu/site/page/a/1194 10 publications and 10 ppts;
  Specimen Care – A global preanalytical resource centre sponsored by BD

References and Links

- Fraser CG. Biological Variation: From Principles to Practice. AACC Press, 2001
- Rustad P et al. The Nordic Reference Interval Project 2000: recommended RIs for 25 common biochemical properties. Scand J Clin Lab Investigation 2004; 64:271-284.
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- Lang T. Reference Intervals: The GB data. Clin Biochem 2011;44: 477-8
- Al-Bori A. 10 Most frequently asked questions about Reference Interval (RI) and Biological Variation (BV) July 2012. https://www.westgard.com/faq-ri-bv.htm
- Miller WG et al. Harmonization: the Sample, the Measurement, and the Report. Ann Lab Med 2014;24:187-97.
- Jones GRD. Validating common reference intervals in routine laboratories. Clinica Chimica Acta 2014;432:119-21
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- Lang T, Croal B. National minimum retesting intervals in pathology. (MRIs). The Royal College of Pathology (UK) or the ACB (UK). 2015
- Adeli K, Higgins V et al. Biochemical Marker Reference Values across Pediatric Adult and Geriatric Ages: ….CHMS Clin Chem 2015;61(8):1049-62.
- Plebani M. Harmonization in laboratory medicine: Requests, samples, measurements and reports. Crit Rev Clin Lab Sci. 2016;53(3):184-96.
- https://www.westgard.com/biodatabase1.htm

SESSION OUTLINE

1. Definitions and Explanations
2. Pre-analytical, analytical and post-analytical considerations
3. Pros and cons of hRIs
4. International initiatives to harmonize reference intervals
5. For what tests are hRIs commonly developed?
6. Biological variation considerations in result interpretation

What is the difference between MU and RU?

What is the difference between MU and RU? ?

Definitions and Explanations:

hRI = harmonized reference interval

…i.e. across laboratories, methods, instruments, manufacturers

…i.e. comparable results irrespective of where, when or how!

RI = locally – determined reference intervals

…i.e. full CLSI protocol (n=120 per partition)

…i.e. CLSI validation protocol (n=20) for transference from previous local reference interval or manufacturer-specific or instrument-specific (kit insert)

…i.e. based on method comparison (slope, intercept)

How does the laboratory convey the source(s) of their reference intervals to their users?

?

Other Definitions and Explanations:

Harmonization: is the process of ensuring that results from
different laboratories using
different methods
are *equivalent*
within clinically meaningful limits.

a) Includes "standardization" of methods to produce
equivalent results from
different laboratories using
different methods using
traceable calibration to reference methods.

b) Includes methods that can't be calibrated by traceability to a reference method.

AACC White Paper, July 2015

Standardization at *pre-analytical phase:*

- Terminology - test name, acronym = expected analyte
  - Appropriate Utilization: right test, right sample, right time
- Preferred sample type; stability criteria for add-ons
- Time of collection: e.g. importance of fasting; diurnal variation
- Sample collection and transportation
- Time to centrifugation requirements by analyte

- Patient preparation directions pre-sampling;
- Collection and documentation of pertinent patient information that is linked with results as necessary.
  - E.g. FBG – fasting blood glucose as its own test

- Reflexive or inclusive testing
  - E.g. Include urine creatinine with pregnancy and DOA tests:
    "Urine creatinine < 2 µmol/L…potential FN…suggest repeat".
- Minimal repeat intervals for appropriate testing frequency (UK) (MRIs) (UM = utilization management)

Standardization at *analytical phase:*

- Indices (hemolysis, lipemia, icteris)– settings, interpretation; result reporting
- Calibrator and calibration (traceability)
- Assay conditions (e.g. 37^{o}C, IFCC co-factors)
- Quality control practices that function similarly to ensure long term consistent performance:
  - Allowable bias and precision between calibration and reagent lots that meets total error allowable (TEa)
- EQA and PT programs – use of AMMs/target values; recognition of different methods
- Other potential factors to consider: LRLs, autoverification

Standardization at *post-analytical phase:*

- **Result reporting**
  - Units; number of significant decimals; critical values
  - Information that aids or affects interpretation:
    - fasting, interferences, urine dilution
- **Results are interpreted by comparison with:**
  - Reference intervals (RIs)
  - Medical decision limits (DLs)
  - Target Values (TVs)
  - Previous patient results (RCV)
- **Results are used for different purposes:**
  - Diagnosis of disease
  - Monitoring disease progression or treatment efficacy

Should results be flagged if they are outside of TVs or DLs?

Why Might hRIs be a Good Thing?

From the physician's and the patient's perspective:

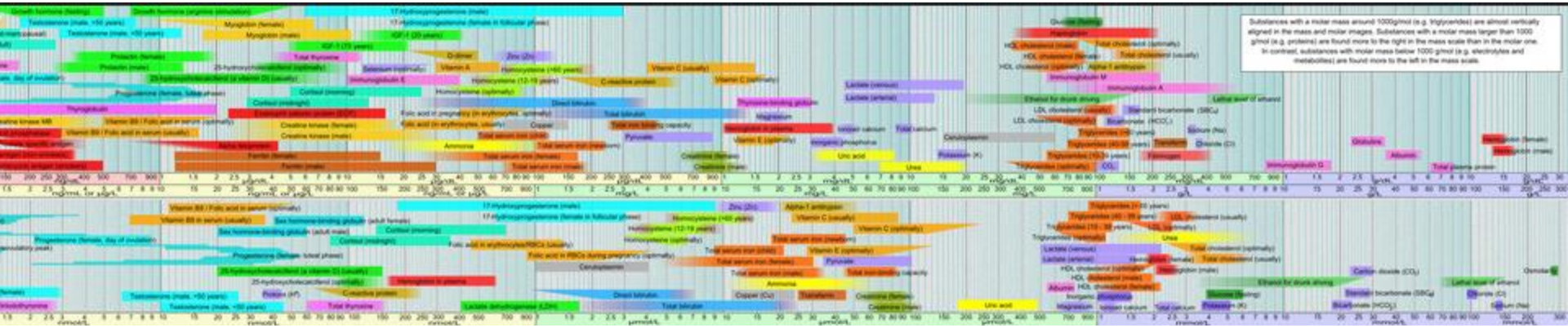
- hRIs promote consistent result interpretation, which may:
  - Standardized care, and
  - Reduce the risk of misdiagnosis and of unnecessary follow-up testing
- Combining results from different laboratories in electronic patient records (EMRs) is not effective without hRIs.
- Physicians need to consider results from different laboratories (e.g. community labs and hospital labs), and may end up using results interchangeably
- Consultation of "Dr. Google" and favourite lab handbooks (eg http://mayomedicallaboratories) is already occurring.

Might heterogeneous RIs contribute to diagnostic error? ?

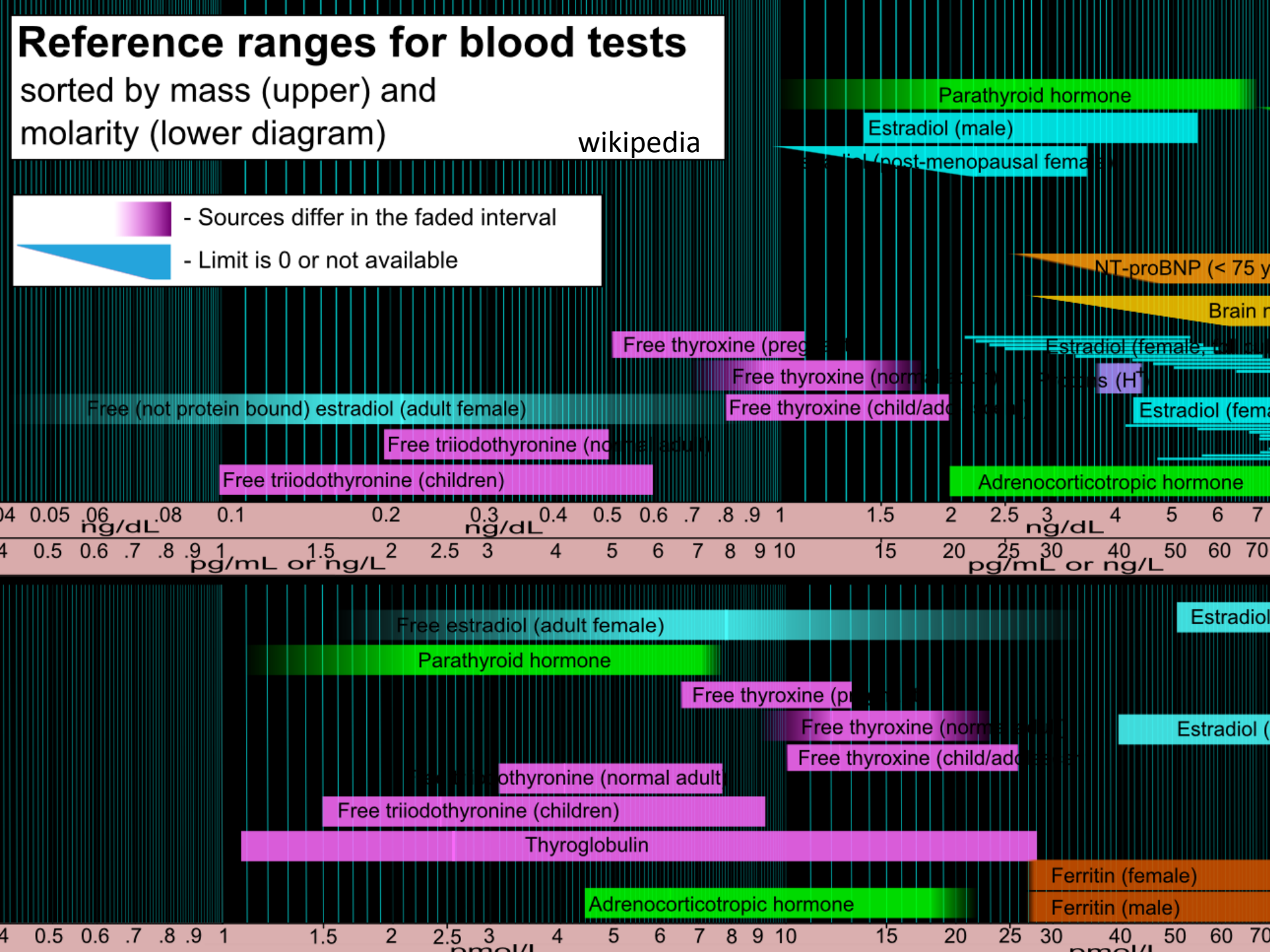
http://www.amamanualofstyle.com/page/si-conversion-calculator

Table 2. Selected Laboratory Tests, With Reference Ranges and Conversion Factors

Analyte	Specimen	Reference Range, Conventional Unit	Conventional Unit	Enter Quantity	Conversion Factor (Multiply by)	Reference Range, SI Unit	Conversion Result	SI Unit	Convert
Acetaminophen	Serum, plasma	10-30	µg/mL		6.614	66-200		µmol/L	< >
Acetoacetate	Serum, plasma	<1	mg/dL		97.95	<100		µmol/L	< >
Acetone	Serum, plasma	<1.0	mg/dL		0.172	<0.17		mmol/L	< >
Acid phosphatase	Serum	<5.5	U/L		16.667	<90		nkat/L	< >
Activated partial thromboplastin time (APTT)	Whole blood	25-40	s		1	25-40		s	< >
Adenosine deaminase	Serum	11.5-25.0	U/L		16.667	190-420		nkat/L	< >
Adrenocorticotropic hormone (ACTH)	Plasma	<120	pg/mL		0.22	<26		pmol/L	< >
Alanine	Plasma	1.87-5.89	mg/dL		112.2	210-661		µmol/L	< >



Reference Ranges - wikipedia


Reference ranges for blood tests
sorted by mass (upper) and
molarity (lower diagram)
wikipedia
- Sources differ in the faded interval
- Limit is 0 or not available
Parathyroid hormone
Estradiol (male)
NT-proBNP (< 75 y
Brain n
Estradiol (female;
Free thyroxine (preg
Free thyroxine (norm
Free thyroxine (child/ad
Free (not protein bound) estradiol (adult female)
Free triiodothyronine (no
Free triiodothyronine (children)
Adrenocorticotropic hormone
ng/dL
pg/mL or ng/L
Free estradiol (adult female)
Parathyroid hormone
Free thyroxine (pr
Free thyroxine (norm
Free thyroxine (child/ad
Free triiodothyronine (children)
Thyroglobulin
Ferritin (female)
Ferritin (male)
Adrenocorticotropic hormone

Why Might hRIs be a Good Thing?

From the Laboratory Professional's perspective:

- Determining local RIs is time consuming and expensive (e.g. age/sex partitioning)
- Selection of healthy "reference" populations is a challenge.
  … determining RIs for some endocrine tests is beyond most labs!
- Analysis may occur over only 1 reagent or calibration lot, with 1 calibration!
  … need to ensuring no long-term bias shifts or changes in precision occur!
- Consider the 90% CIs around the local RIs or hRIs. *Is rounding reasonable?*
- Are manufacturer-specific RIs perfect? *…what you we know about them?*
- Local RIs were originally based on the expectation of significant "geographical" differences, such as genetic, racial or environmental differences.
  … some RIs for CK are only valid for Caucasians – do we state this?

Do you think most local RIs are justified or ensure optimal patient care?

?

Reference Intervals: CLSI C28-A3c
Gary Horowitz. et al. (3rd Ed, Nov 2008)

- ***1st CHOICE***: establish the RI from reference *healthy* individuals

  n=120 per sex/age partition; use nonparametric statistics

  Determine the 90% confidence limits of the RL's
- Some labs may use fewer samples, or make assumptions about distributions and partitions, or "refer to studies done many decades ago, when both the methods and the population were different."

"… in practice, very few laboratories perform their own RI studies."

RECCOMMEND: **Verify** RI established elsewhere by ***transference***.

- "Most" laboratories do this now against the manufacturer insert RI or a reference laboratory's RI (n=20)

  Assumption: comparability of the population and

  pre-analytical factors (e.g. specimen collection and handling).

Manufacturer-Specific RIs ….

- Minimal information often provided:
  - 90% confidence intervals of RIs not usually provided
  - age partitioning process not described
  - missing ranges for certain ages (e.g. pediatrics, geriatrics)
  - validation over time or several lots and combinations of reagents, calibrators and calibrations is not always described
  - changes in RIs with lot reformulations not always performed
- Insert usually says:
  - "laboratory should determine its own reference intervals"
  - "This normal range is suggested as a guideline and each laboratory should establish a normal range appropriate to their patient populations, giving due consideration to **age**, **gender**, **geographical location** and their **clinical practice**."
  - "…establish its own normal range ***which may be unique*** to the population it serves depending upon geographical, patient, **dietary**, or **environmental factors**."

…This minimizes the manufacturers' responsibilities!

COMMENTARY

The Case for Common Reference Intervals

Jones, GRD et al. Clin Biochem Rev 2004;25: 99-104

- **current paradigm:** each laboratory to determine its own RIs
- **we believe that this approach:**
  - not performed well in many laboratories; and, is excessively expensive
  - does not best serve the medical community
  - especially for use by **electronic databases (EMRs)**.
- **preferable option is to develop and apply:**
  - common RIs (= hRIs), common reporting formats, and assay standardisation wherever this is possible.

"…these are neither trivial nor simple issues, however, we believe that failure to achieve this goal where technically possible will be a failure of the pathology profession to meet the challenges of the modern health community."

Factors supporting hRIs:

1. Already use clinical decision limits which are not determined or validated in individual laboratories, e.g. *glucose, lipids, HbA1c.*
2. hRIs are being developed by other international chemistry organizations.
3. Advances in assay standardization.

Difficulties with common reference intervals:

1. True local population differences. *[may be?]*

Practical issues with developing hRIs:

1. Organise and support a body to oversee the project.
2. Agree on statistical approaches to development and application of hRIs.
3. Obtain quality local data for hRIs.
4. Consensus on format of results and hRIs.
5. Publish hRIs and criteria for use by laboratories.
6. Overcome inertia in laboratories and encourage wide-spread adoption.

Jones, GRD et al. Clin Biochem Rev 2004;25: 99-104

Evidence from an EQA/PT program in Australia for magnesium suggests that "differences in reference intervals between laboratories is not related to assay standardisation".

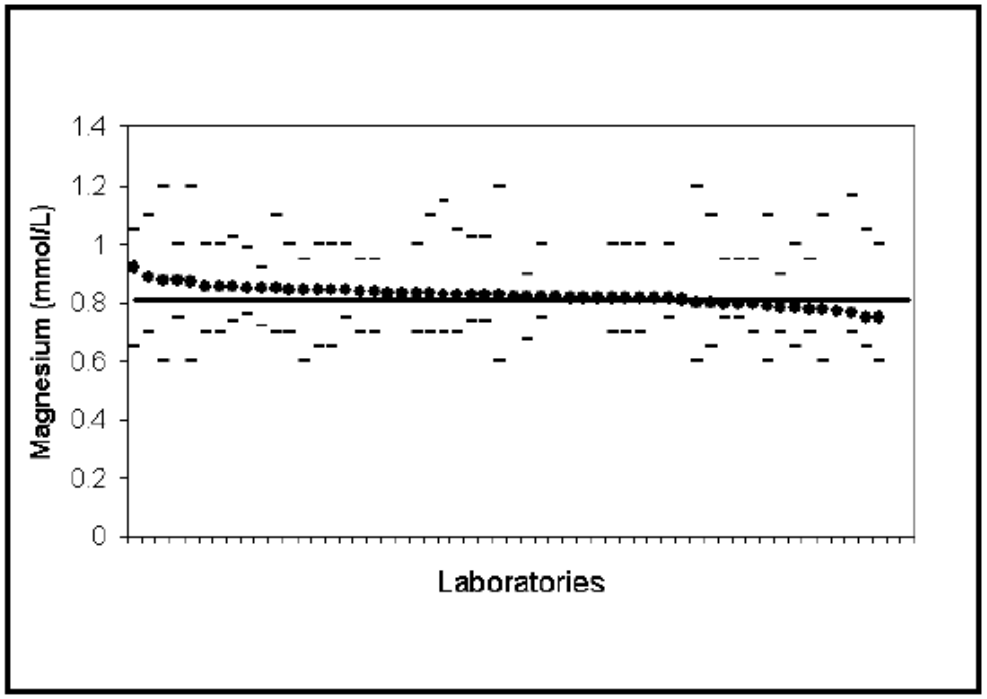


Figure 1. IMEP-17 data for Australian and New Zealand participants for magnesium. Magnesium concentration of supplied sample, average of 10 measurements (filled circles); upper and lower reference limits (dashes), and the IMEP target value (unbroken line). The data is sorted in order of decreasing values for measured magnesium. Note there is no correlation between measured magnesium concentration and the stated reference limits.

Jones, GRD et al. Clin Biochem Rev 2004;25: 99-104

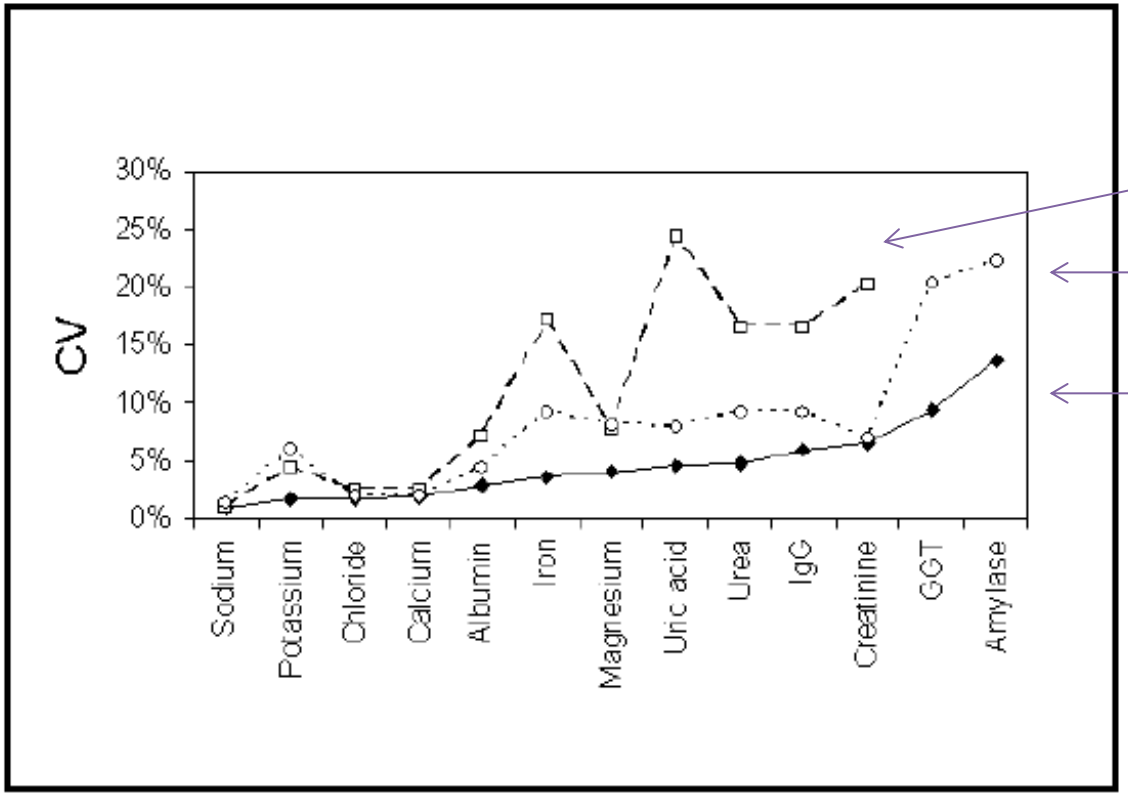


Figure 2. IMEP-17 data for Australian and New Zealand participants. Plot of between-laboratory variation for analyte concentration (closed diamonds) and upper (open circles) and lower reference interval values (open squares). Variation expressed as the CV. Note no data is supplied for lower reference intervals for GGT and amylase due to the use of "less than" formats in some laboratories.

Between-laboratory variation (%CV) by test for:

LRLs (lower RL)

URLs (upper RL)

Sample measurement

Jones, GRD et al. Clin Biochem Rev 2004;25: 99-104

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journal homepage: www.elsevier.com/locate/clinbiochem

National Survey of Adult and Pediatric Reference Intervals in Clinical Laboratories across Canada: A Report of the CSCC Working Group on Reference Interval Harmonization

Khosrow Adeli[a,*], Victoria Higgins[a], David Seccombe[b], Christine P. Collier[c], Cynthia M. Balion[d], George Cembrowski[e], Allison A. Venner[f], Julie Shaw[g], on behalf of the CSCC Reference Interval Harmonization (hRI) Working Group

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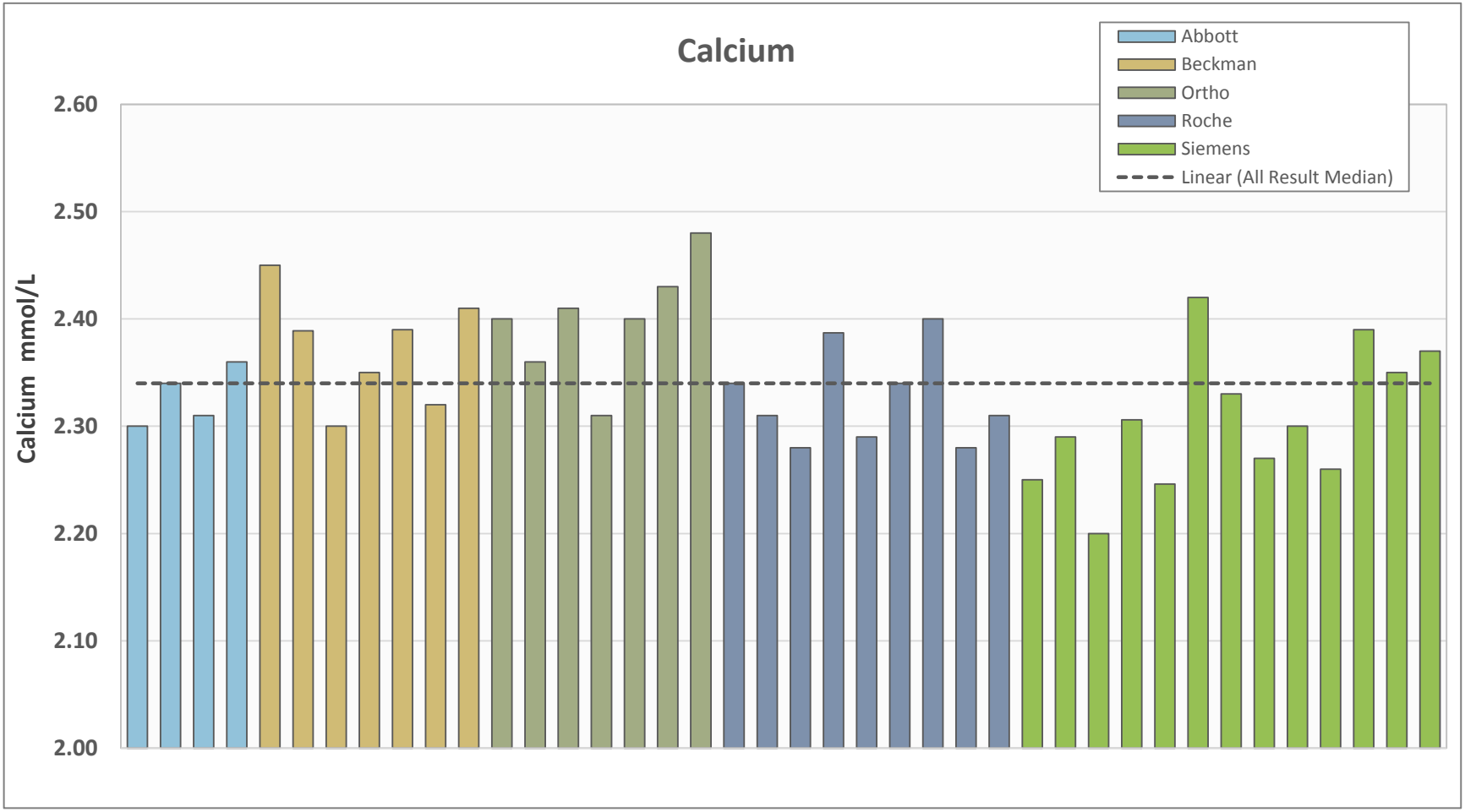
[b] CEQAL, Vancouver, BC, Canada
[c] Kingston General Hospital and Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada
[d] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada
[e] Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada
[f] Calgary Laboratory Services and Department of Pathology and Laboratory Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[g] Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Eastern Ontario Regional Laboratories Association and University of Ottawa, Ottawa, ON, Canada

A commutable sample was sent as a baseline comparison to volunteer laboratories across Canada, April 2016



n=40

Mean=2.341 **Min=2.200** **SD=0.062**

Median=2.340 **Max=2.480** **%CV=2.6**

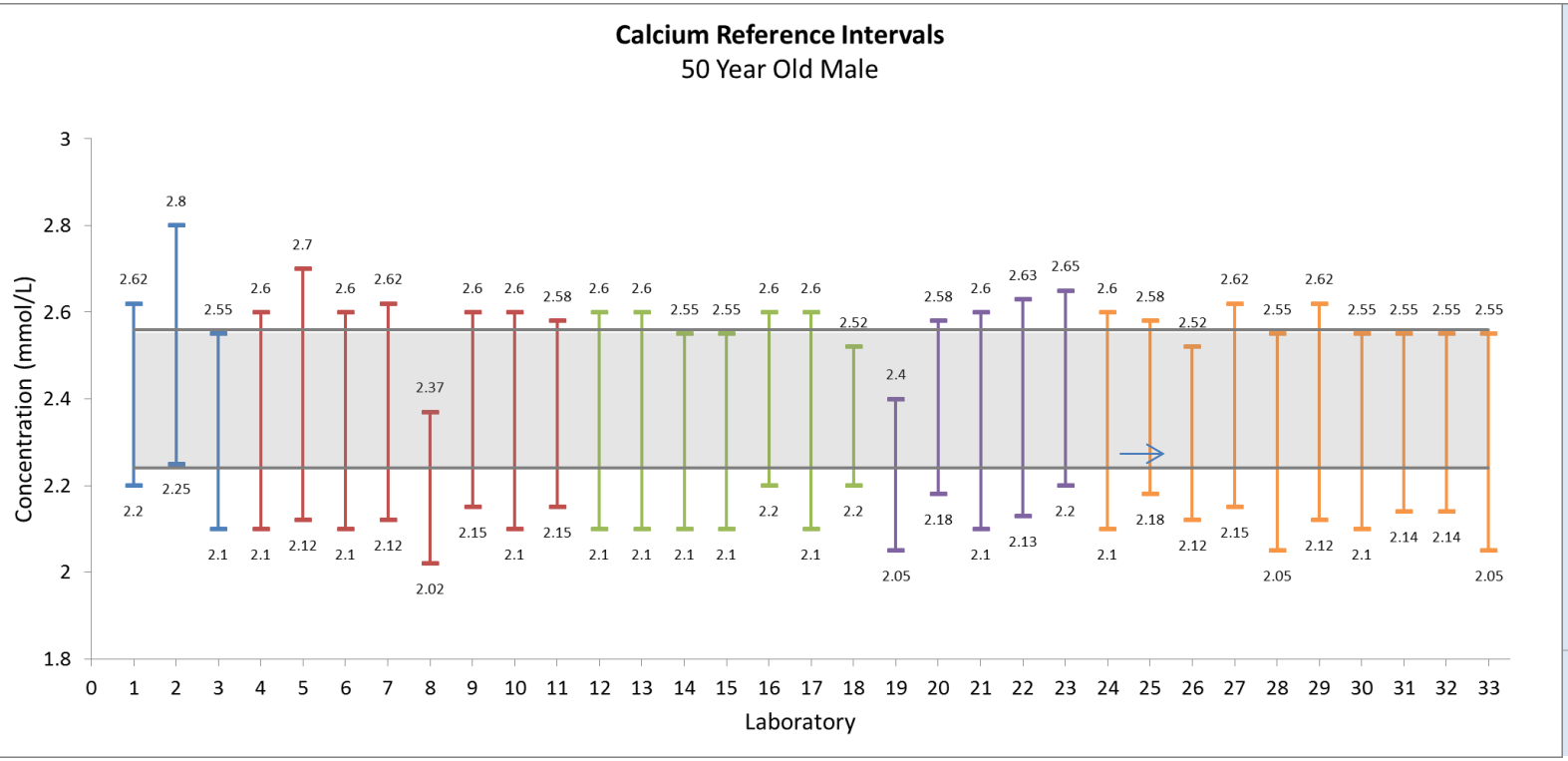
Results reported in 1, 2 or 3 decimals

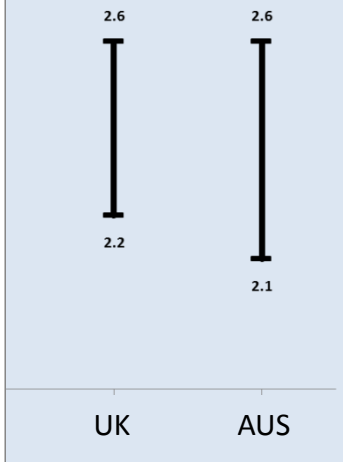
Adeli K, Higgins V et al. Clin Biochem 2017

"Calcium Reference Intervals Used in Clinical Practice Across *Canada, 2016*"

Comparison Across Clinical Chemistry Instruments

Example: 50 YEAR OLD MALE





Abbott
Beckman
Ortho
Roche
Siemens
Harmonized

Canadian Population Reference Intervals (CHMS)-*Recommended*

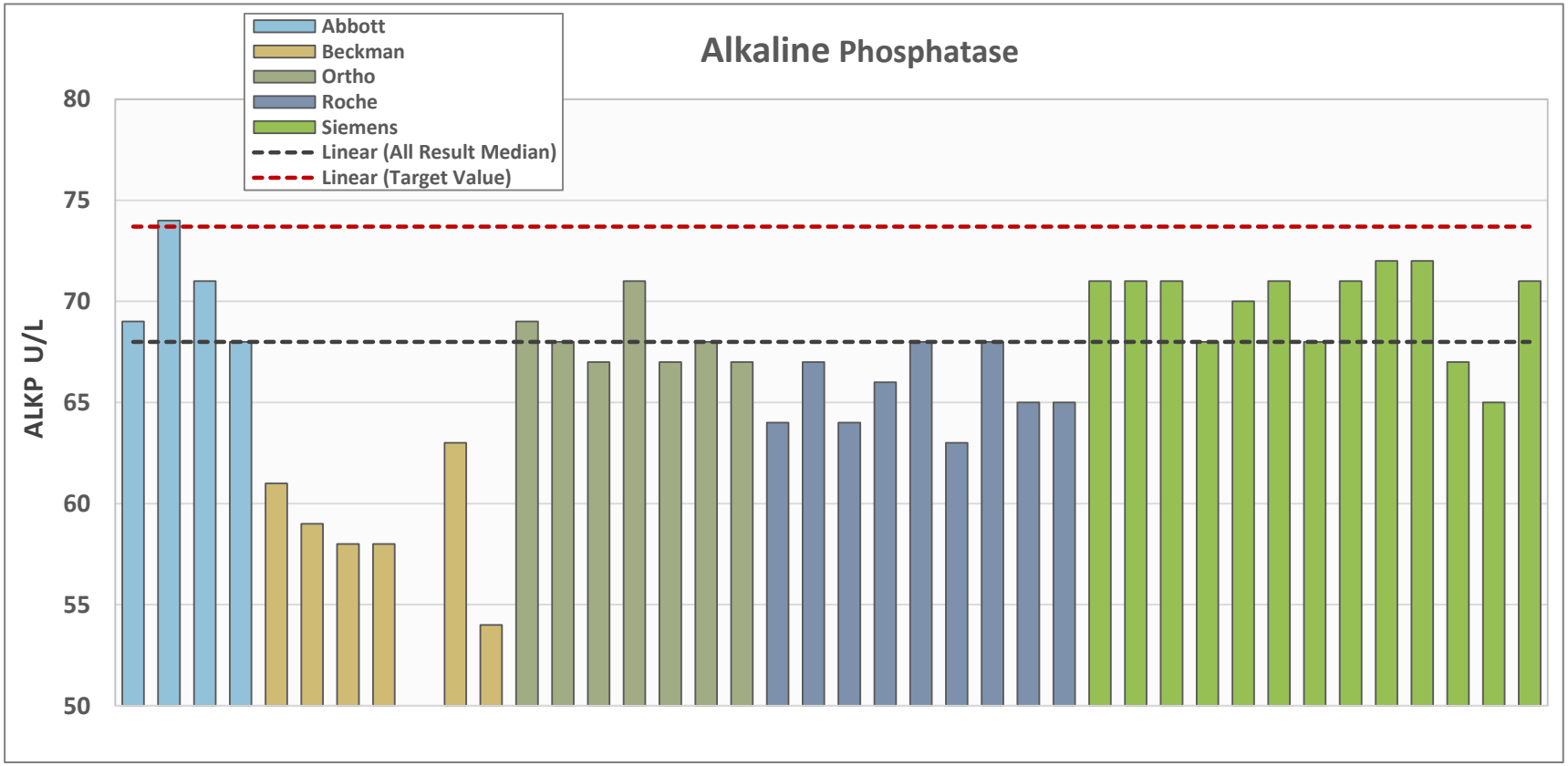
Upper Limit % Difference: **2.0%**

Lower Limit % Difference: **2.3%**

UK = UK Pathology Harmony Project; AUS = Australasian Harmonized Reference Intervals (AHRIA)

Adeli K, Higgins V et al. Clin Biochem 2017

A commutable sample was sent as a baseline comparison to volunteer laboratories across Canada, April 2016



Target=73.7 **n=39**

Mean=66.9 **Min=54** **SD=4.43**

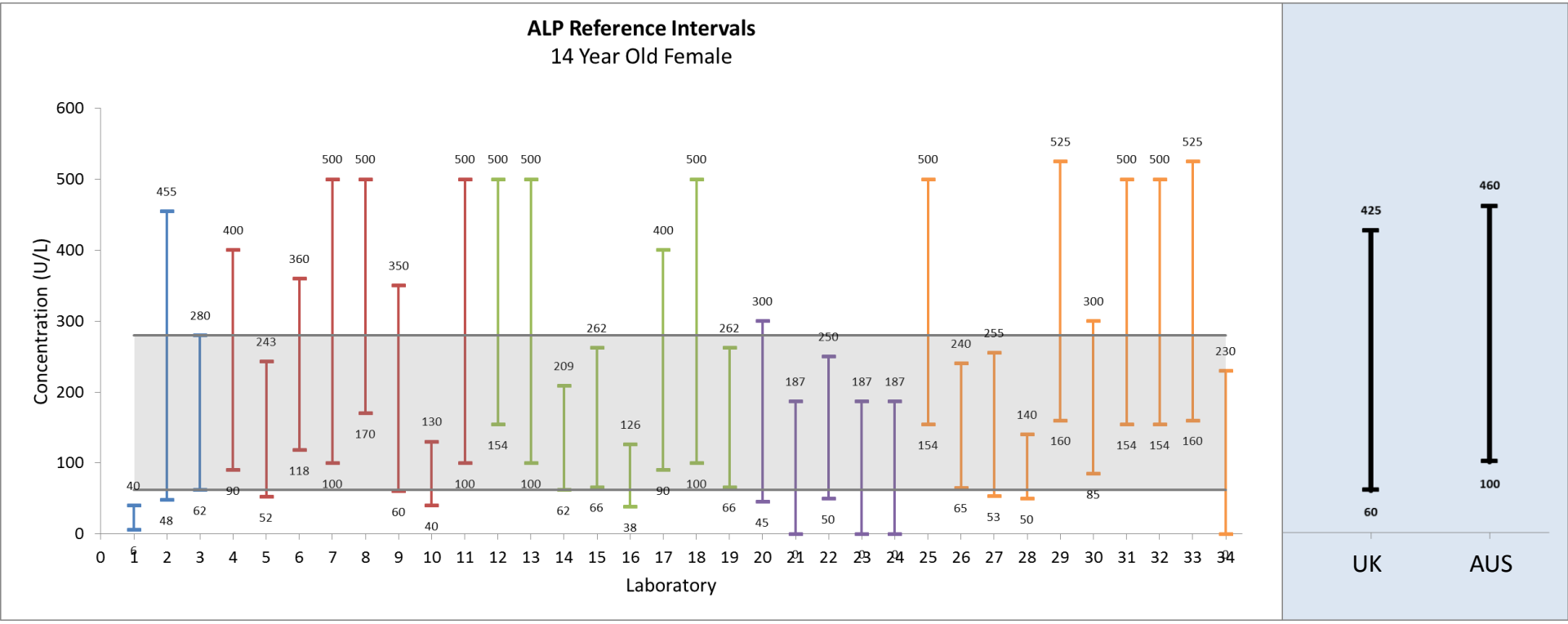
Median=68.0 **Max=74** **%CV=6.6**

Adeli K, Higgins V et al. Clin Biochem 2017

"Alkaline Phosphatase Reference Intervals Used in Clinical Practice Across *Canada, 2016*"

Comparison Across Clinical Chemistry Instruments

Example: 14 YEAR OLD FEMALE



- Abbott
- Beckman
- Ortho
- Roche
- Siemens
- Harmonized

Canadian Population Reference Intervals (CALIPER)-*Recommended*

Upper Limit % Difference: **41.9%**

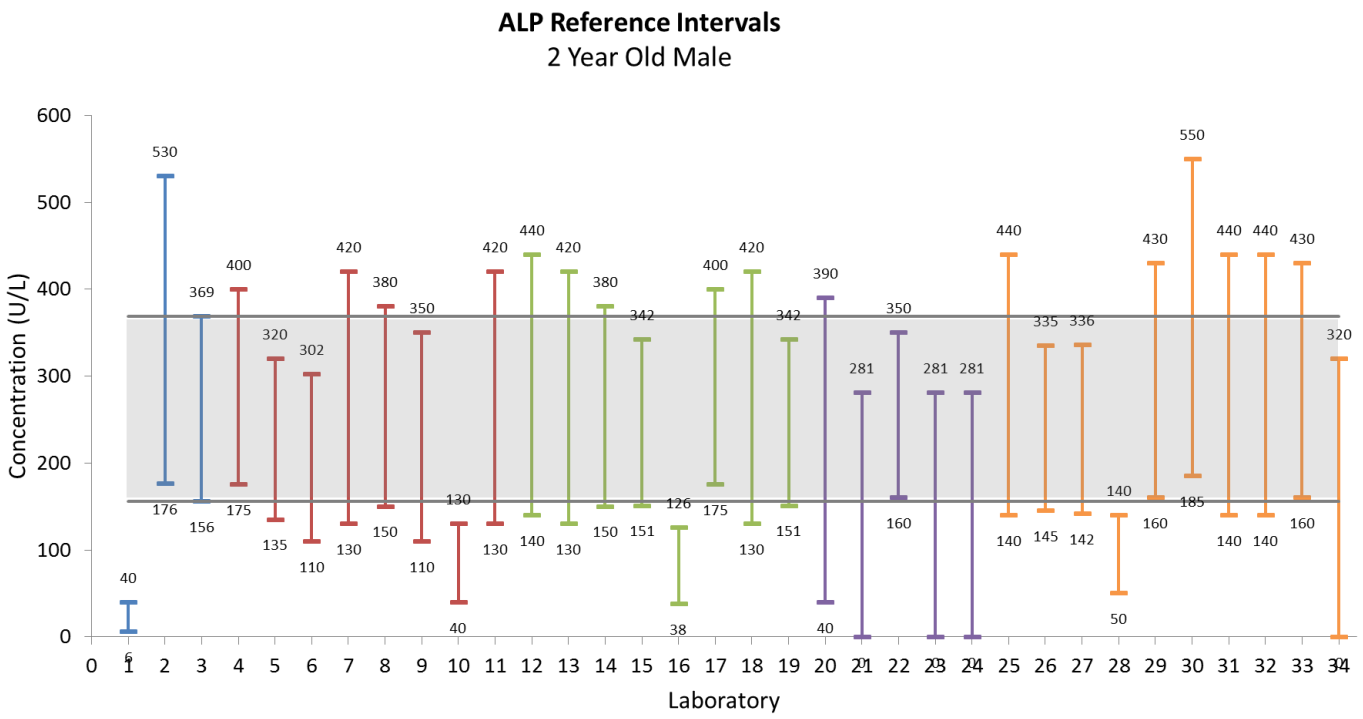
UK = UK Pathology Harmony Project; AUS = Australasian Harmonized Reference Intervals (AHRIA)

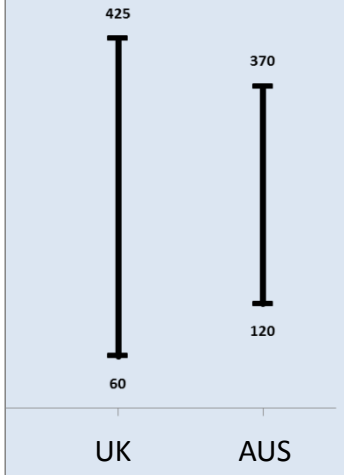
Adeli K, Higgins V et al. Clin Biochem 2017

"Alkaline Phosphatase Reference Intervals Used in Clinical Practice Across *Canada, 2016*"

Comparison Across Clinical Chemistry Instruments

Example: 2 YEAR OLD MALE





Abbott
Beckman
Ortho
Roche
Siemens
Harmonized

Canadian Population Reference Intervals (CALIPER)-*Recommended*

Upper Limit % Difference: **27.9%**

UK = UK Pathology Harmony Project; AUS = Australasian Harmonized Reference Intervals (AHRIA)

Adeli K, Higgins V et al. Clin Biochem 2017

Clinical Chemistry 61:8
1049–1062 (2015)

Biochemical Marker Reference Values across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey

Khosrow Adeli,[1*] Victoria Higgins,[1] Michelle Nieuwesteeg,[1] Joshua E. Raizman,[1] Yunqi Chen,[1] Suzy L. Wong,[2] and David Blais[3,4]

Clinical Chemistry 61:8
1063–1074 (2015)

Complex Reference Values for Endocrine and Special Chemistry Biomarkers across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey

Khosrow Adeli,[1*] Victoria Higgins,[1] Michelle Nieuwesteeg,[1] Joshua E. Raizman,[1] Yunqi Chen,[1] Suzy L. Wong,[2] and David Blais[3,4]

SickKids

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Hospital > CALIPER Project >

Listen

CALIPER across Canada

CALIPER = Canadian Laboratory Initiative on Paediatric Reference Intervals Database

CALIPER began as a multi-centre initiative, coordinated by The Hospital for Sick Children (SickKids) in collaboration with six other children's hospitals located in Ottawa, Hamilton, Montreal, St. John's, Saskatoon and Vancouver.

In collaboration with these sites, we were able to establish a current and accurate database of reference intervals (normal values) that represent Canada's children and youth—multi-ethnic males and females from ages birth to 18 years. The database is currently being used by physicians for the interpretation of common

Select the following

Instrument: * Abbott

Abbott
Ortho
Roche
Siemens
Beckman DxC
Beckman AU

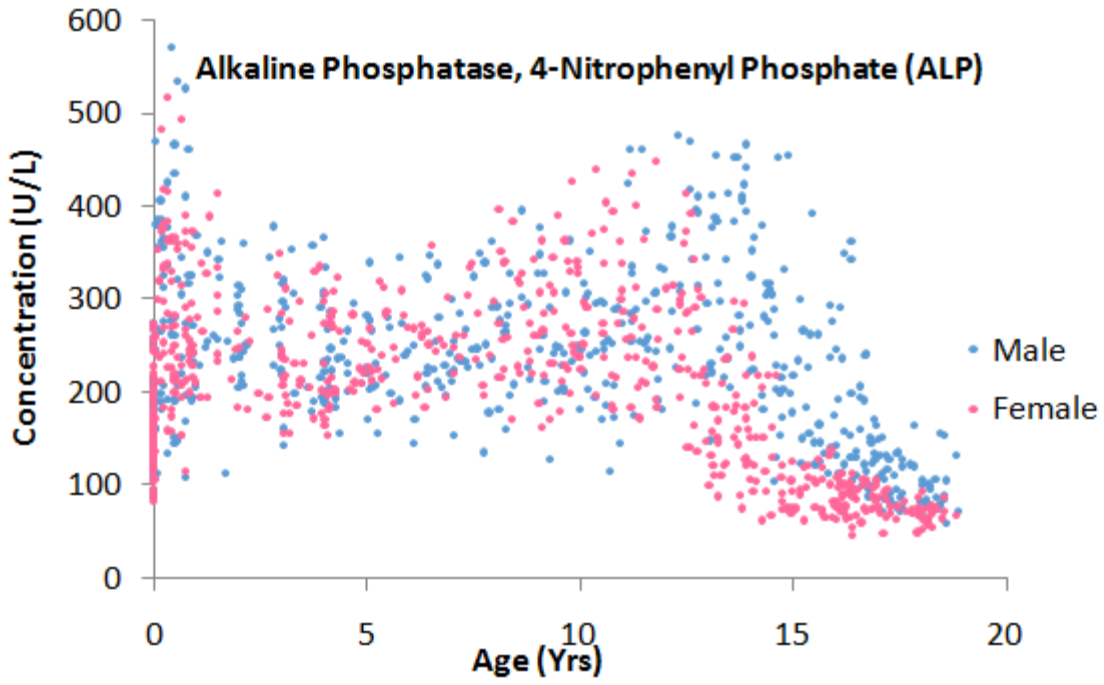
Units: * SI Conventional

Analyte: * Alkaline Phosphatase 4-Nitrophenyl Phosphate (ALP)

Submit

Print

Alkaline Phosphatase 4-Nitrophenyl Phosphate (ALP) (U/L)



Female Reference Intervals

Age	Lower Limit	Upper Limit	Samples	Lower CI	Higher CI	95th Percentile
0 - 14 days	90	273	155	(83 - 104)	(257 - 274)	
15 days - < 1 year	134	518	147	(108 - 153)	(466 - 570)	
1 - < 10 years	156	369	391	(145 - 170)	(362 - 391)	
10 - < 13 years	141	460	154	(114 - 171)	(424 - 476)	
13 - < 15 years	62	280	68	(56 - 68)	(254 - 301)	
15 - < 17 years	54	128	74	(50 - 58)	(122 - 133)	
17 - < 19 years	48	95	40			

Male Reference Intervals

Age	Lower Limit	Upper Limit	Samples	Lower CI	Higher CI	95th Percentile
0 - 14 days	90	273	155	(83 - 104)	(257 - 274)	
15 days - < 1 year	134	518	147	(108 - 153)	(466 - 570)	
1 - < 10 years	156	369	391	(145 - 170)	(362 - 391)	
10 - < 13 years	141	460	154	(114 - 171)	(424 - 476)	
13 - < 15 years	127	517	66	(112 - 149)	(481 - 546)	
15 - < 17 years	89	365	64	(84 - 97)	(329 - 388)	
17 - < 19 years	59	164	54			

Legend

This table provides a summary of age and sex-partitioned pediatric reference intervals for serum alkaline phosphatase (ALP). Whole-blood samples were collected from healthy children and adolescents (newborn to 18 years of age) from a multiethnic population and measured on the Abbott ARCHITECT c8000 analyzer.

http://www.sickkids.ca/caliperproject/
caliper.support@sickkids.ca

Implementation of **hRIs** by an Individual Laboratory

Approach:

- Review local RIs and their 90% confidence intervals (Cis), and compare these to the proposed hRIs (or the manufacturer-specific RIs) and their 90% CIs.
  Are the RIs different or do the 90% CIs overlap?
- Review EQA/PT data (e.g. Bias and TEa)
  - Is analyte compared to AMM or target value? Should it be? (consider all medically important concentrations)
  - Is there a significant bias with your method or your laboratory?
- Retrospective local data mining – what is current false positive (FP) and false negative (FN) rate? What would these rates be for hRIs?
  - Discuss with local clinicians if clinically significant.

Calcium, Total (mmol/L) - VIAL 1

Results Assessed by All Methods Mean ⟶ ±5.0%

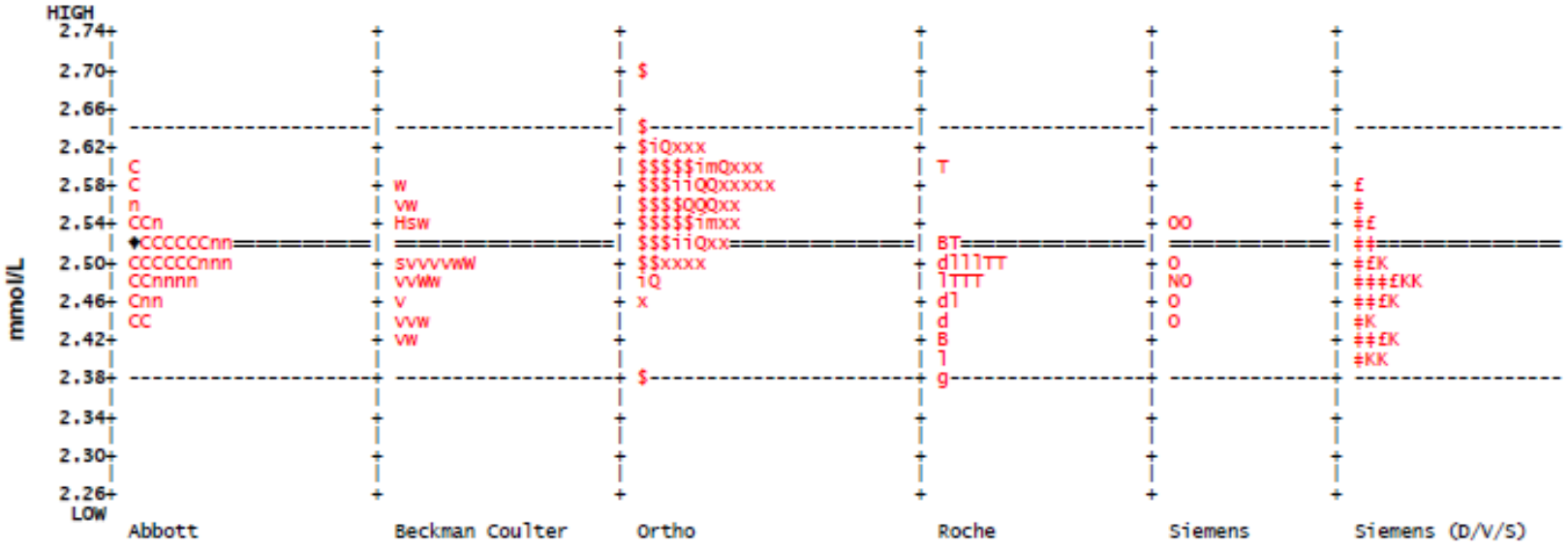
Your Method: Arsenazo III Dye (71), Abbott Architect C4000,C8000,C16000 (758), Abbott (10)

Your Assessment	Result	Plot Code	Assigned Value	Deviation from AV (%)	SDI	PAD Score
	2.51	n	2.51	0.0	0.00	0

	Total Results	Total Stats	Mean	Median	SD	CV (%)	UAV	Min Result	Max Result	Allowable Limits
All Methods	179	179	2.51	2.500	0.060	2.4	0.006	2.37	2.69	2.38 - 2.64
Reagent										
Abbott	35	35	2.50	2.500	0.029	1.2		2.43	2.59	
Beckman Coulter	23	23	2.49	2.490	0.051	2.0		2.41	2.57	
Ortho	67	67	2.56	2.560	0.046	1.8		2.37	2.69	
Roche	19	19	2.48	2.480	0.042	1.7		2.38	2.60	
Siemens	7	7	2.49	2.480	0.038	1.5		2.44	2.53	
Siemens (D/V/S)	28	28	2.46	2.470	0.054	2.2		2.39	2.57	

Calcium, Total - VIAL 1

N: 179 Grouped By Reagent All Methods' Mean: 2.51 Allowable Limits: 2.38 - 2.64



Creatinine (IDMS Std) (µmol/L) - VIAL 1

Results Assessed by Reference ⟶ ±9 µmol/L if <100 µmol/L, ±9.0% if ≥100 µmol/L

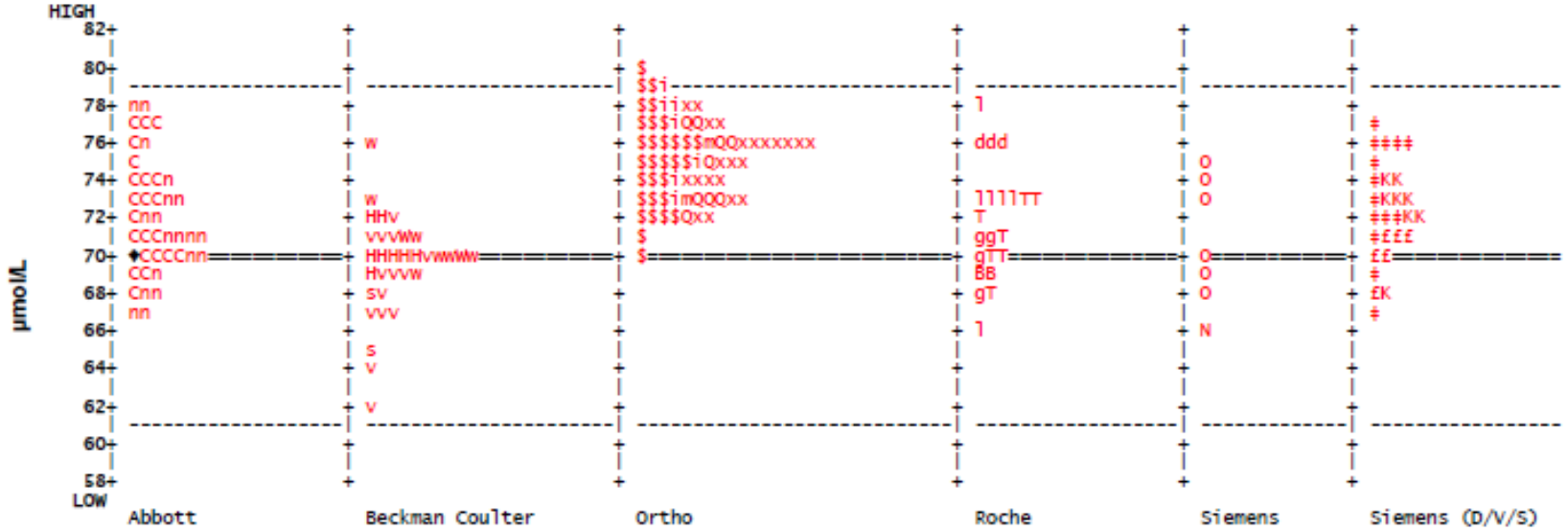
Your Method: Enzymatic (102), Abbott Architect C4000,C8000,C16000 (758), Abbott (10)

Your Assessment	Result	Plot Code	Assigned Value	Deviation from AV (%)	SDI	PAD Score
	70	n	70	0.0	0.00	0

	Total Results	Total Stats	Mean	Median Assigned Value	SD	CV (%)	UAV	Min Result	Max Result	Allowable Limits
All Methods	203	203	73	73.0	70	3.4	4.7	0.6	62	80	61 - 79
Reagent										
Abbott	42	42	72	71.0		2.9	4.0		67	78	
Beckman Coulter	33	33	70	70.0		1.6	2.3		62	76	
Ortho	71	71	75	75.0		2.4	3.2		70	80	
Roche	22	22	72	71.5		3.0	4.2		66	78	
Siemens	7	7	71	70.0		3.8	5.4		66	75	
Siemens (D/V/S)	28	28	72	72.0		2.8	3.9		67	77	

Creatinine (IDMS Std) - VIAL 1

N: 203 Grouped By Reagent Assigned Value: 70 Allowable Limits: 61 - 79



Great minds have already spent much time on harmonization & hRIs

Nordic initiative (2004)

United Kingdom (2009, 2011)

Australia and New Zealand (2012 - 2016)

USA

Japan, Spain….

IFCC TASK FORCE ON RIs and DLs

Local adoption of hRIs will be perceived to be:

- *an improvement in laboratory service*
- *progressive and consistent with other countries*

Taylor & Francis
healthsciences

Scand J Clin Lab Invest 2004; 64: 271–284

The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties

P. RUSTAD,* P. FELDING,† L. FRANZSON,‡ V. KAIRISTO,§ A. LAHTI,¶
A. MÅRTENSSON,‖ P. HYLTOFT PETERSEN,** P. SIMONSSON,††
H. STEENSLAND‡‡ & A. ULDALL§§

TABLE I. Common reference intervals for the Nordic countries suggested by NORIP project group.

		CAL		NFKK Ref. Serum X	Quality goal	NORIP Reference intervals														
								Calculated										Suggestions		
								Serum					Plasma (Li heparin)					Serum		Plasma
Component	Unit	Target value	Source	Target value	Bias	Gender	Age	Low	90% CI	High	90% CI	N	Low	90% CI	High	90% CI	N	Low	High	Low High
Albumin	g/L	40.52	NTP	41.5	2.1%	FM	18–39	36.5	36.3–36.7	47.9	47.5–48.4	1010	35.8	35.2–36.3	47.2	46.9–48.1	452	36	48	
							40–69			45.4		1248			45.4	45.1–45.9	589		45	
							≥70	34.4	33.5–34.8		45.2–45.6	450	34.5	33.8–34.9			244	34		
Bilirubin	µmol/L	8.5	DGKC	8.97	15.1%	FM	≥18	4.7	4.5–5.0	24	23.1–25.1	2738	5.1	4.7–5.4	26	24.3–28.4	887	5	25	
Calcium	mmol/L	2.266	NTP	2.325	1.4%	FM	≥18	2.17	2.17–2.18	2.51	2.50–2.52	2569	2.15	2.14–2.16	2.48	2.47–2.50	1204	2.15	2.51	
Calcium, albumin corrected[1]	mmol/L	2.282	See calcium and albumin	2.321	1.2%	FM	18–49	2.20	2.19–2.21	2.47	2.46–2.48	1385	2.17	2.16–2.18	2.46	2.45–2.49	623	2.17	2.47	
							≥50			2.53	2.52–2.54	1149			2.52	2.49–2.53	558		2.53	

5 countries, 102 labs, 25 analytes, 25 samples from healthy subjects

pathologyharmony.co.uk

working to harmonise standards in UK pathology

Pathology Harmony

Pathology Harmony is an initiative working towards harmonisation in UK pathology laboratories which was established in January 2007.

If you wish to comment, join or contribute ideas, please email secretary@pathologyharmony.co.uk

Haematology

Haematology units of measurement

For the latest statement on the standardisation of reporting units for haematology, issued December 2012, please click here.

The information regarding the standardisation, issued in April 2012, can be viewed here

Full access to site

Access to the full site is restricted. If you already have a user name and password enter here.

New users should email info@pathologyharmony.co.uk and will receive an email with a username and password

FAQ No 3

www.pathologyharmony.co.uk/

Phase 1 Results

The table below shows the recommendations that resulted from the work of the first phase of Pathology Harmony. Only those proposals which met with overwhelming acceptance at the final meeting in November 2007 have been included in the recommendations.

Reference intervals and units – in adults, non-pregnant

Code No.	Analyte	Lower/upper limit	Units
PH 07 001	Serum Sodium	133 – 146	mmol/L
PH 07 002	Serum Potassium	3.5 – 5.3	mmol/L
PH 07 003	Serum Urea	2.5 – 7.8	mmol/L
PH 07 004	Serum Chloride	95 – 108	mmol/L
PH 07 005	Serum Bicarbonate	22 – 29	mmol/L
PH 07 006	Serum Phosphate	0.8 – 1.5	mmol/L
PH 07 007	Serum Magnesium	0.7 – 1.0	mmol/L
PH 07 008	Serum Albumin	35 – 50	g/L
PH 07 009	Serum Total Protein	60 – 80	g/L
PH 07 013	Serum Osmolality	275 – 295	mmol/kg

…also some hRIs for pediatric results, TDM and 24 hour urine quantitations

Results

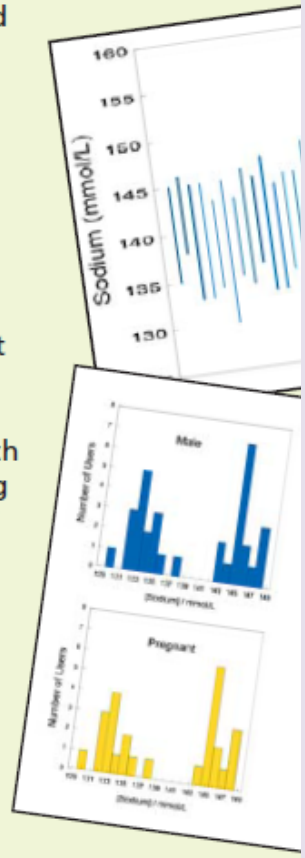
Variation in serum sodium in West Midland laboratories is shown in the figures. When the analytical platforms were reviewed it was found that the variation in reference intervals was not related to analytical platforms. Indeed, many laboratories used identical equipment and reagents but had small variations in the reference intervals they quoted for serum sodium. Population studies in no way explained variation.

Further work looking at variation between laboratories was brought back to the meeting and it was clear that the major reason for variation was simply historical, with no scientific foundation. Following this conclusion 'pragmatic science' was applied whereby the group considered the variations at the bottom and top end of the reference intervals and came to a consensus view on a sensible reference interval to propose.

Suggested referece interval: 133-146 mmol/L

Conclusion

The evidence was
final action learni
unanimously appr



Tim Lang Clin Biochem 44(2011)477-478

AACB – Australasian Association of Clinical Biochemists

Professional Development

Harmonisation

Scientific and Regulatory Affair Committee (SRAC)

- Committee
- Working Parties
- QC Subcommittees
- Useful Tools
- Harmonisation
  - Reference Intervals (& Workshops)
  - Methods
  - Units and Terminology
  - Critical Laboratory Results

BACKGROUND

towards pathology harmonisation

"In recent times it has become clear to the users and commissioners of hospital diagnostic services that there are differences in reference intervals and units of measurement between laboratories.

We, in the profession, recognise that there are sometimes genuine scientific reasons for these differences, for example differences in local populations or analytical methodology.

However, **it is important to differentiate those analytes for which there is no clearly identifiable reason for a difference."** (UK Pathology Harmony Group, Clinical Biochemistry Outcomes, January 2011)

One of the AACB's major strategies is to facilitate the validation and implementation of "harmonised" reference intervals initially for the more commonly requested tests, across Australasia.

We see this as a significant step forward in providing improved patient care and outcomes.

Common reference intervals will become increasingly relevant with the advent of the electronic medical record.

Committee

Jill Tate (Chair)

Julie Ryan

Kristina Barancek

Narelle Hadlow

Australia and New Zealand

Consultation…*verification…*consensus..
implementation…*verification*

- 19 of 27 chemistry analytes could have hRIs, (commutable sample analysis 2010)
- 5 annual Stakeholder workshops (2012 – 2017)
- Spreadsheet validation tool for labs
- hRIs are slightly wider - reduced sensitivity
  - calculate FP Rate and FN Rate; economic impact
- *12 tests adopted for adults; 10 tests for pediatrics*

Clin Biochem Rev 2014; 35(4)

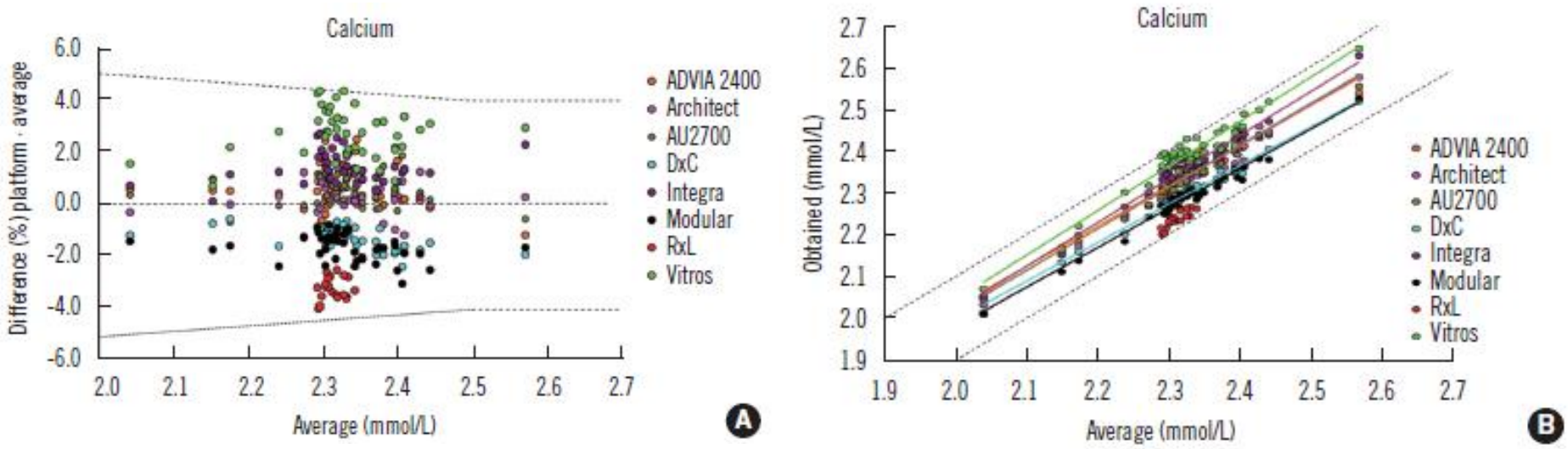


Fig. 5. Assessment of suitability of a common reference interval for different routine measurement procedures for **calcium** using data from **33 reference interval subjects** measured by 24 laboratories using 8 platforms (at least 3 laboratories participated per platform) and acceptance criteria from the Royal College of Pathologists of Australasia Quality Assurance Program [45]. (A) almost all results for calcium fell within the allowable limits of agreement **(±0.1 mmol/L up to 2.5 mmol/L and ±4% when >2.5 mmol/L variation from the all methods mean**) (B) the regression lines were all within the allowable limits of performance for the eight routine measurement procedures that were evaluated. (A) is used with permission from reference 42. (B) is used with permission from a study performed by the Harmonisation Group of the Australasian Association of Clinical Biochemists (www.aacb.asn.au/professionaldevelopment/harmonisation).

Our specific objectives

✓ to improve the harmonization of results from clinical laboratory measurement procedures for measurands (analytes) that do not have reference measurement procedures

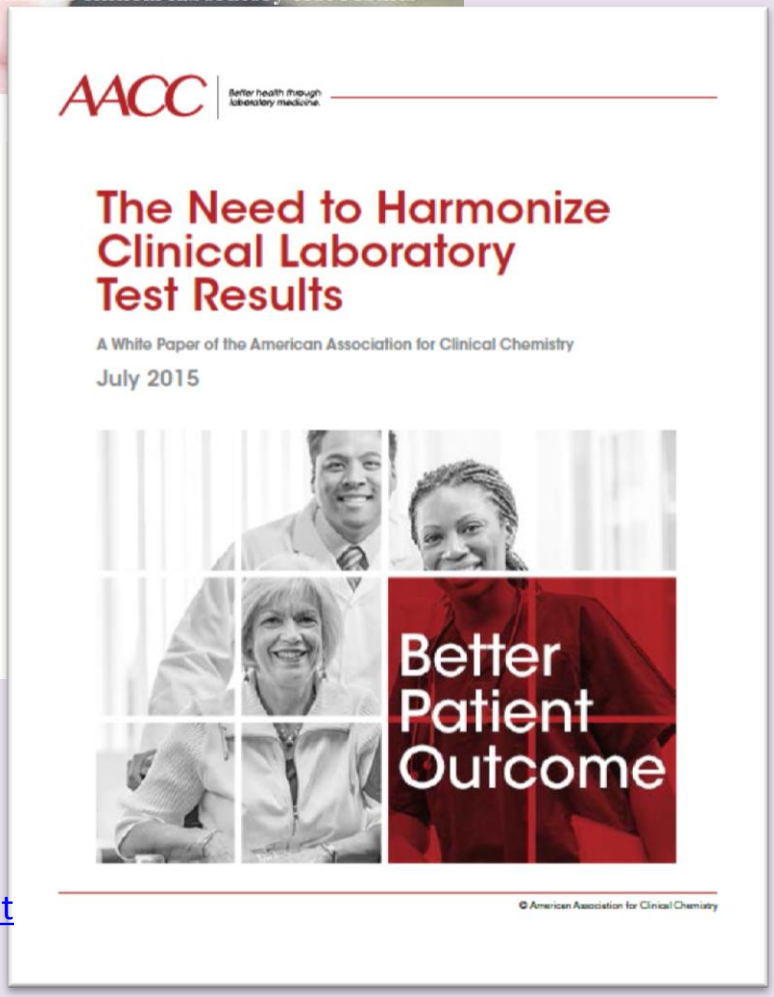
✓ to provide a resource center for information on global activities to harmonize and standardize clinical laboratory measurement procedures

Organization

Operating Procedures for the International Consortium for Harmonization of Clinical Laboratory Results describe the program. The governing body is a Council made up of organizations from around the world that contribute financially to support the administration of the program. A Harmonization Oversight Group (HOG) is responsible to manage the harmonization activities.

Interested stakeholders may become Organizational Members of the consortium or join the Strategic Partners Group to support and contribute to the harmonization activities.

The AACC is the secretariat for administration of the program.



AACC and International efforts

http://www.harmonization.net/
http://www.harmonization.net/media/1026/harmonization_white_paper_715.pdf

The Need to Harmonize Clinical Lab Results

July 2015 – AACC White Paper (Greg Miller, Gary Meyers, Vince Stine)

- **The Problem:** Some lab tests lack a gold standard, and results vary from lab to lab.

- **The Need:** Accurate and Comparable Clinical Laboratory Test Results
  - Patients and physicians **assume** that results are comparable and consistently interpreted
  - "When lab tests don't give consistent results, patients who don't actually have a disease can receive unnecessary treatment, and patients with a disease might not receive appropriate treatment."

Consolidated & Further Continuing Appropriations Act of 2015

In 2014, the *Senate Labor, Health and Human Services, Education and Related Agencies Subcommittee* identified the harmonization of clinical laboratory test results as a critical issue for improving patient care.

… this bill urged the CDC to work with the laboratory community to create uniform test results to reduce medical errors to improve the quality of care and to empower patients.

AACC White Paper, July 2015

Reducing the Misdiagnosis of Chronic Kidney Disease

Prior to a voluntary standardization effort in British Columbia in 2004 , creatinine results varied greatly between laboratories. This was especially true for results that fell within normal to near-normal ranges, in which accurate test interpretation is critical in classifying a patient's kidney function.

The pilot study found that among 107 participating laboratories, 124 different instruments from six different manufacturers were being used. At baseline, the average measurement error was 24%. After harmonization, the level of variation dropped to 8.7%. The authors calculated that extending harmonization throughout the province could reduce false-positive rates of creatinine results by 84%, thereby preventing 450,000 people from being misdiagnosed and treated for stage 3 (moderate) kidney disease.

Costs of Non-Harmonized Laboratory Testing

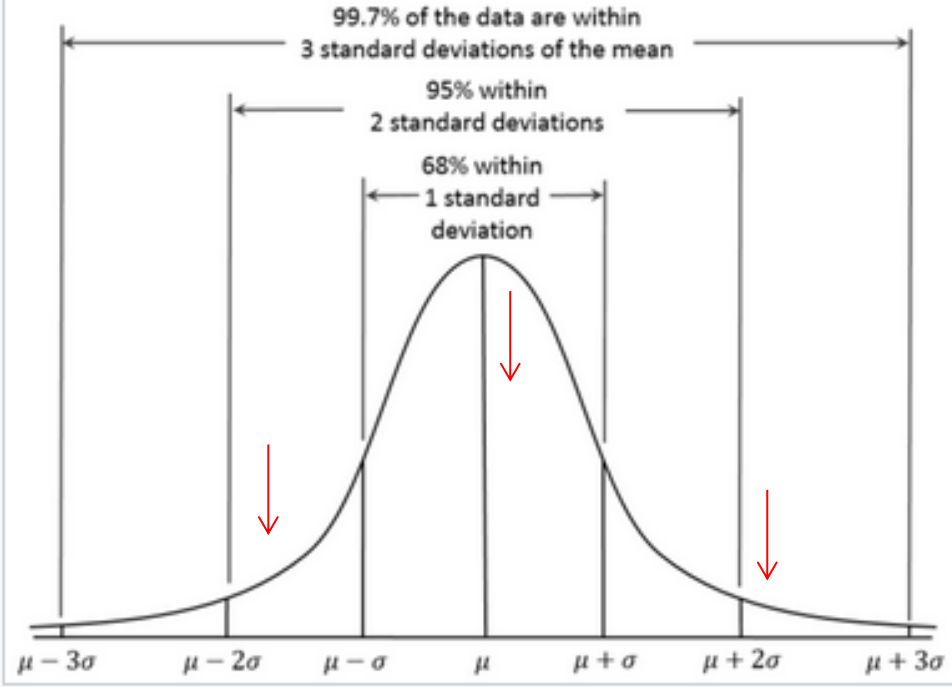
In 2004, a NIST study analyzed calcium results in more than 89,000 patients. Patients in this study had at least one calcium result above the URL of ≥ 8.9 mg/dL in 1998 and 1999 (Calcium RI is 8.9 – 10.1 mg/dL ; 2.23 – 2.52 mmol/L).

The study found that **calibration errors** skewed calcium results in a positive direction by 0.1 to 0.5 mg/dL (i.e higher than they really were) (0.03 to 0.13 mmol/L). These calibration errors were caused by a lack of traceability to standard reference materials, **variations among reagents or calibrator lots**, and changes in instrument readings between calibrations. Such errors produce false positive results for hypercalcemia that lead to unneeded follow-up procedures, including chest x-rays, 24-hour measures of urine calcium, and thyroid imaging, which all increase healthcare costs ***$$$***.

The authors estimated that the **cost of a result that was 0.1 mg/dL higher** than the correct value ranges from **$8 to $31 per patient**, while the cost of a result that was **0.5 mg/dL too high was $34 to $89 per patient**. Given that about 3.5 million patients have calcium tests each year in the USA, the potential *cost of false positive (and false negative) results ranges from $60 million to $199 million per year!*

AACC WHITE PAPER, JULY 2015

An assay with a positive bias may have → more false positives



For the normal distribution, the values less than one standard deviation away from the mean account for 68.27% of the set; while two standard deviations from the mean account for 95.45%; and three standard deviations account for 99.73%.

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Advancing excellence in laboratory medicine for better healthcare worldwide

SD Committees

- Nomenclature for Properties and Units (C-NPU)
- Molecular Diagnostics (C-MD)
- Traceability in Laboratory Medicine (C-TLM)
- Reference Intervals and Decision Limits (C-RIDL)
- Standardization of Thyroid Function Tests (C-STFT)
- Harmonization of Autoimmune Tests (C-HAT)

Reference Intervals and Decision Limits (C-RIDL) IFCC committee

Current Projects:

- Preparation of a publication on RIs for AST, ALT, GGT and ALP
- Collaboration in a multicenter study for the definition of RIs of the most common serum analytes in the Asian population

Corresponding Members, nominated by National Societies:

- Argentina, Australasia, Brasil, **Canada**, Ethiopia, German, India, Italian, Japan, Lithuania, Malaysia, Montenegria, Maroca, **Nepal**, Netherlands, Nigeria, Norway, Pakistan, Phillipines, Poland, South Africa, Sri Lanka, Switzerland, **Turkey**, Uruguay, Vietnam

Corresponding Members, nominated by Corporate Members:

- Abbott Diagnostics, Beckman Coulter, Mitsubishi Chemical Europe, Roche Diagnostics, The Binding Site, Siemens

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Advancing excellence in laboratory medicine for better healthcare worldwide

Scientific Division

- SD Committees
- **SD Working Groups**
- SD Minutes
- Reference Materials
- Project Proposal Form
- SD Documents
- SD Yearly Publications of Interest
- Participation in External Programs and Joint Committees

SD Working Groups

- Standardisation of Hemoglobin A2 (WG-HbA2)
- Standardisation of Carbohydrate-Deficient Transferrin (WG-CDT)
- Standardisation of Albumin Assay in Urine (WG-SAU)
- Standardisation of Pregnancy-Associated Plasma Protein A (WG-PAPPA)
- Growth-Hormone (WG-GH)
- Standardization of Insulin Assays (WG-SIA)
- Standardization of Troponin I (WG-TNI)
- Parathyroid Hormone (WG-PTH)
- CSF-Proteins (WG-CSF)
- Standardization of Bone Marker Assays (WG-BMA)
- Commutability (WG-C)
- Immunosuppressive Drugs (WG-ID)
- Apolipoproteins by Mass Spectrometry (WG-APO MS)
- Pancreatic Enzymes (WG-PE)
- Fecal Immunochemical Testing (WG-FIT)

Current approach to analyte selection

A

- Analytes with reference method (traceable)
- Analytes with an important clinical impact
- Na, K, Cl, Calcium, Phos, Mg, creatinine, TP, TBIL, ALT, ALP, LDH (Glucose,HbA1c,cholesterol) ,FT4

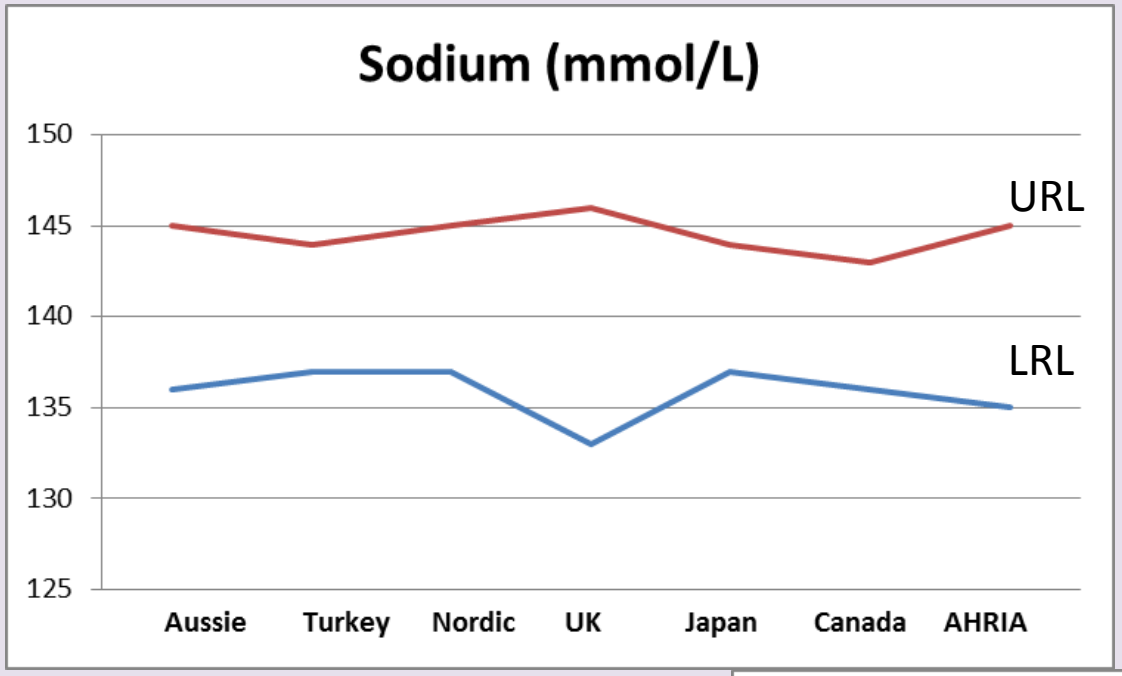
B

- Analytes important to harmonize but are not traceable
- Bicarb, Urea, albumin, urate, AST, CK, GGT, DBIL, OSM, C3, lactate, TSH, hCG, ferritin, transferrin, testosterone, tumor markers (Trigs)

C

- Analytes important in test interpretations (outside above)
- IGF1, vitaminB12, vitamins D, A, E, BNP, troponin, GH, aldosterone, renin, FSH, LH, prolactin, insulin, progesterone, ACTH, cortisol, lipase, blood gases, trace metals, ApoB, ApoA1, Iron, CRP, IgG, IgA, IgM, CBC

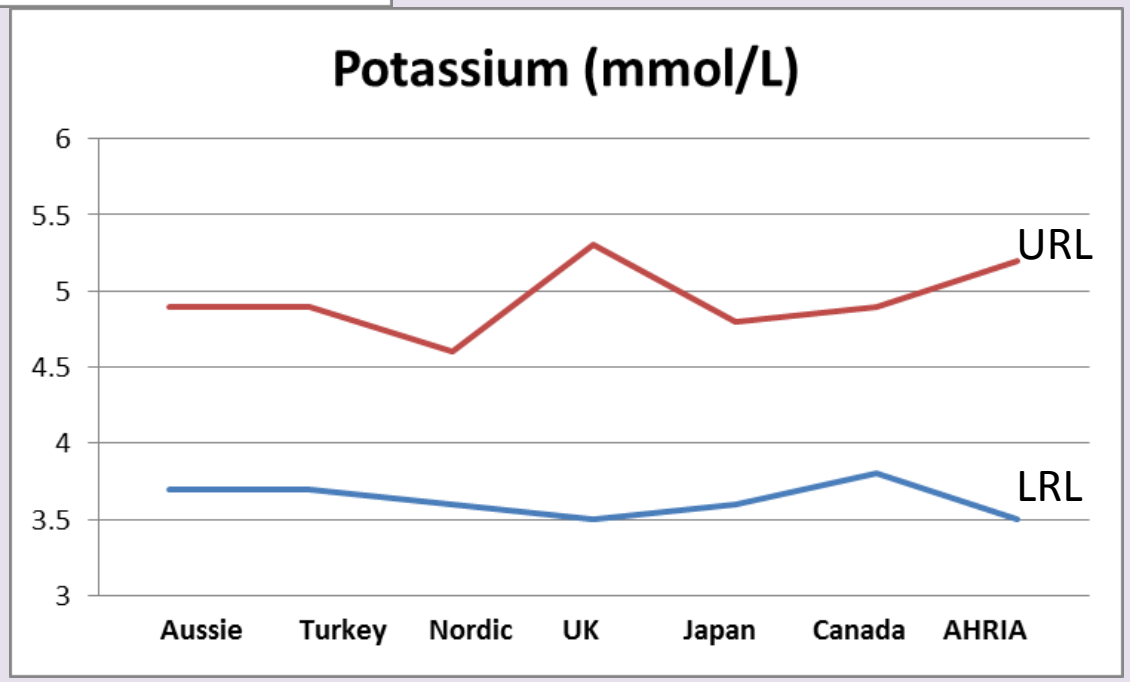
International hRIs: 1-4 or 5 – 7 guidelines



…same reagents, calibrators and instruments worldwide…*and yet!*

Aussie Normals - Architect
Turkey - Architect
Nordic Countries - multiple
United Kingdom - multiple
Japan – 4 main platforms
Canada - Architect
Australasia – 8 main platforms

Direct RI study; consensus RIs



Definitions and Explanations:

BV = biological variation

CVi = within-individual BV (i.e. intra)

CVg = between-individual BV (i.e. inter)

RCV = reference change value $=2.77 \times \sqrt{(CVa^2 + CVi^2)}$

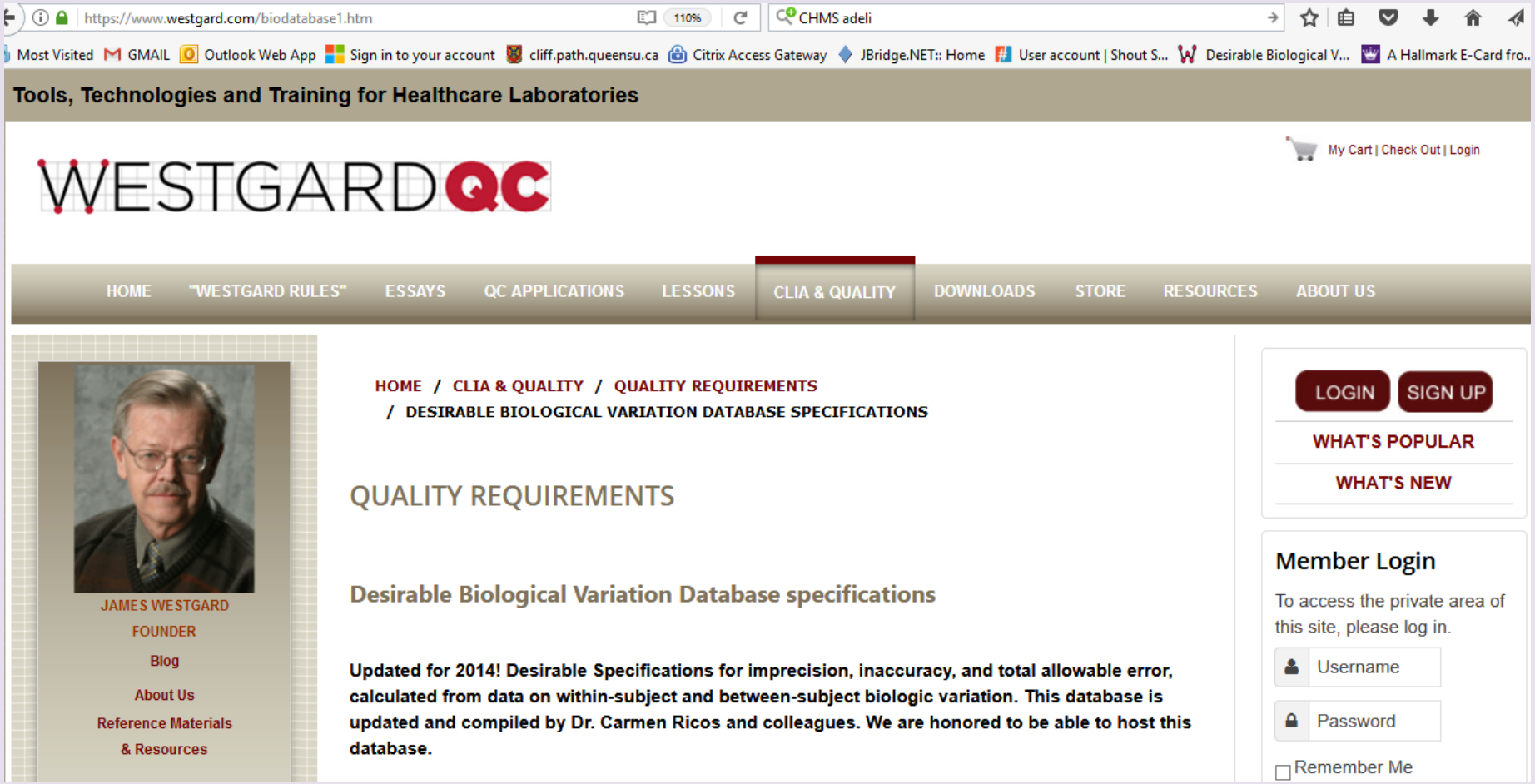
….e.g. a significant change between a patient's serial samples.

II = index of individuality $=CVi / CVg$

….If the **II < 0.6** (CVi << CVg), then comparison of a result to the "population" RI is not as sensitive as it may need to be to detect a significant change in a patient's result.

Why is biological variation information not commonly conveyed by laboratories?

?



https://www.westgard.com/biodatabase1.htm

	Analyte	Number of Papers	Biological Variation		Desirable specification		
			CV_I	CVg	I(%)	B(%)	TE(%)
B-	Erythrocytes, count	7	3.2	6.3	1.6	1.7	4.4
B-	Platelets, count	7	9.1	21.9	4.6	5.9	13.4
P-	Prothrombin time	2	4	6.8	2	2	5.3
B-	Reticulocyte, count	1	11	29	5.5	7.8	16.8
S-	N-terminal (NT)-proBNP	2	10	16	5	4.7	13
B-	Hemoglobin A1 C	8	1.9	5.7	0.9	1.5	3
-	Cholesterol	46	5.95	15.3	2.98	4.1	9.01
S-	Interleukin-8	1	24	31	12	9.8	29.6
S-	Iron	11	26.5	23.2	13.3	8.8	30.7

https://www.westgard.com/biodatabase1.htm

Importance of Personalized Medicine

MY OPINION: The patient is being treated, not the population!

Within-individual variation << between-individual variation

(CVi << CVg) for many chemistry and hematology tests (e.g. 80%).

Patients have their own unique homeostatic set points, and SDs.

A significant difference (**RCV**) may occur for a patient within the "population" RI, and yet the result may still be interpreted as normal.

As laboratory professionals, we know an individual result has a **MU** which is due to imprecision. Physicians actually deal with result uncertainty **(RU),** which is due to an individual's inherent biological variation, and the long-term biases and imprecision of the analytical method(s).

MU is for ISO and Accreditation; RU is for the physician and patient

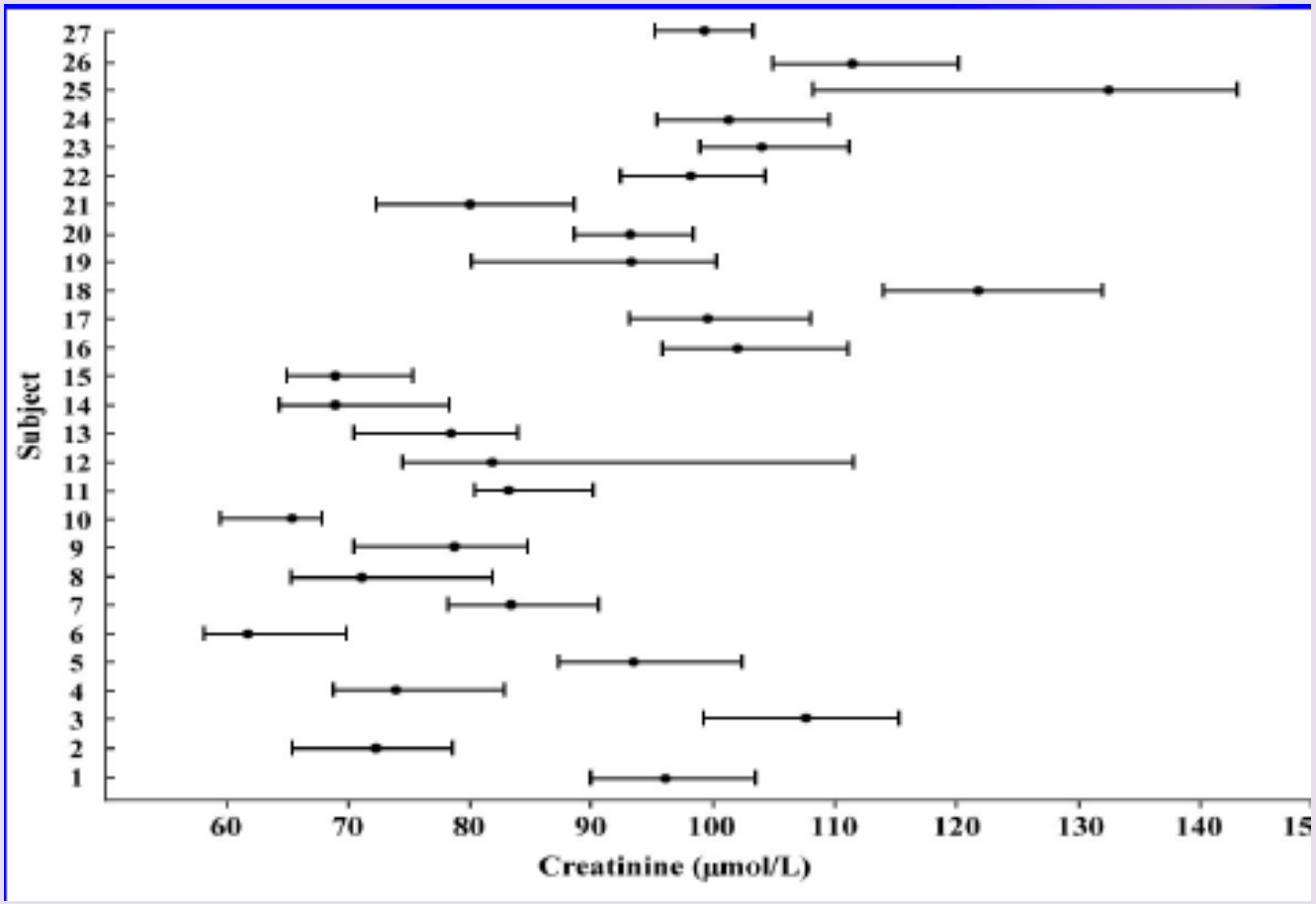
MU is the 95% confidence interval of a single result = 1.96 x CVa

$$RU = 1.96 \times \sqrt{(CVa^2 + CVi^2)}$$

A Thoughtful Responder

There are relatively few tests for which MU is truly relevant. In most tests pre- analytic and natural biological variation are far greater determinants of result variation than MU. Nevertheless, clinician awareness of MU is not where it should be, there is work to do

https://www.westgard.com/mu-uslabs-speak-out.htm



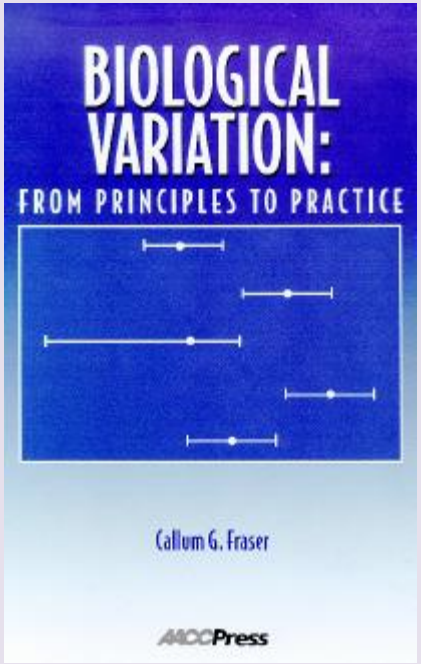
Men

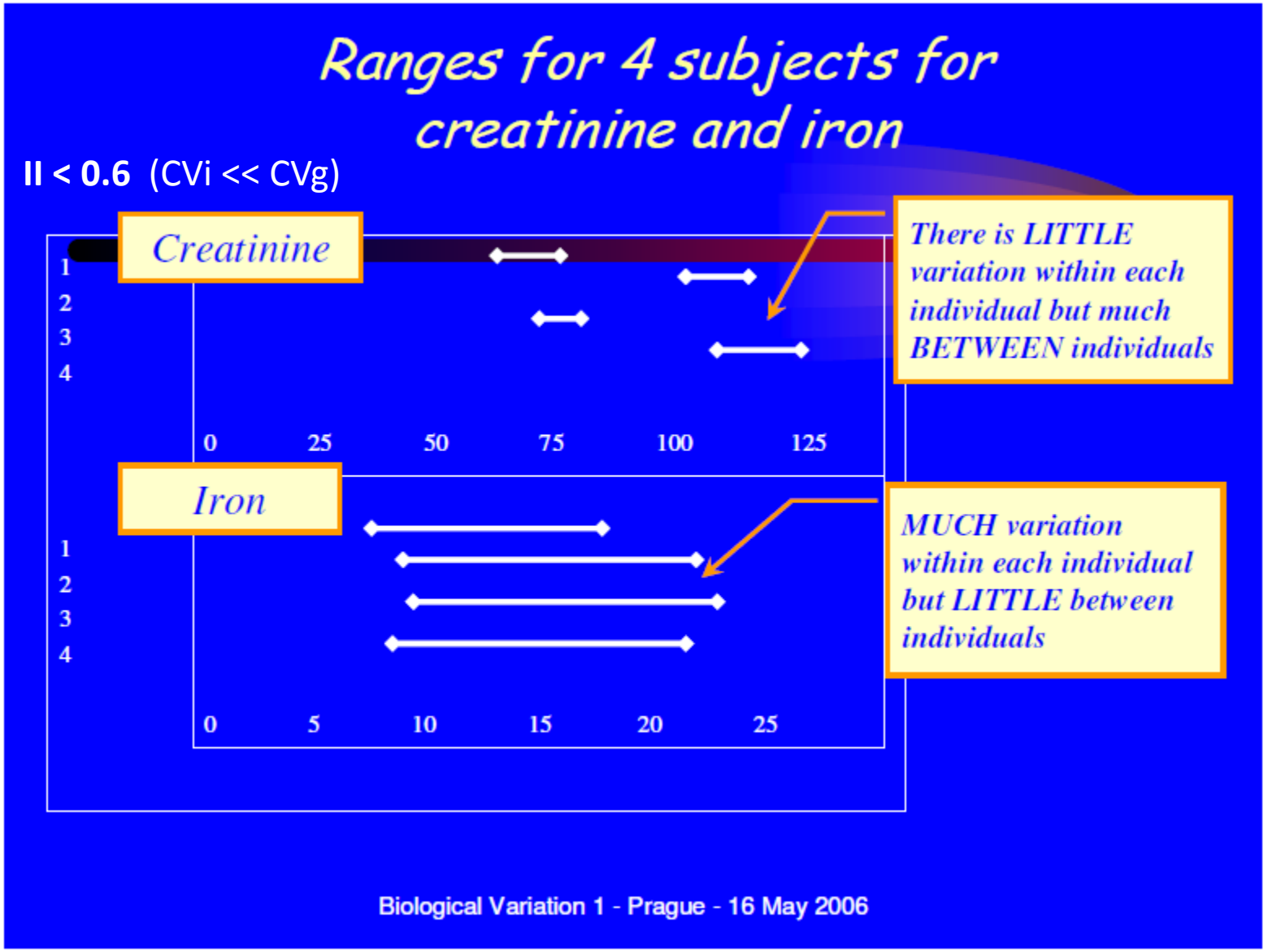
Women

We have different homeostatic set points!

Some people could increase significantly and still be within the RI!

Available at aacc. org





Callum Fraser, 2006

KGH: Index of Individuality = [sqrt(CVi^2 + CVa^2)]/CVg

<0.4	0.4 - 0.59	0.6 - 0.99	1.0 - 1.4	>1.4
		Potassium	Sodium	Lactate
Creatinine	Uric Acid	Calcium	Chloride	pH
LDL	Cholesterol	Magnesium	Calcium, Ionized	
	HDL	Phosphate		pCO2
	Triglycerides	Urea		
B2Microglobulin	Glucose	Bilirubin, Conju	Osmolality	
Homocysteine	Myoglobin	Bilirubin, Total		
ALP	ALT	AST		
CKMB	CK	LD	Total Proteins	
Amylase		Lipase		
GGT	Prealbumin	Albumin		
Ig G,A,M		Protein, Total	Ferritin	
C3, C4	TT4	FT4	Iron	
Folate & RBC	Cortisol	TSH		
DHEAS	Testosterone	CRP		
SHBG	Fructosamine	HbA1c		
FSH	LH			
Prolactin				
CEA		Creatinine (U)	Potassium (U)	Protein (U)
PSA		Alb(U)	CrClearance	Sodium (U)

Critical Difference (RCV) between serial samples necessary for a significant change (< 0.05) based on both analytical and biological variation KGH 2008

5%	10%	20%	30%	40%	50%	60%	70%	80%	100%
NA	K	GLU	UREA					LAC	
CL	CA	CREA	PHOS						
	MG	HCO3							
		URIC							
OSM	pH	pCO2							
		ALP	AMY	GTT				ALT	
			AST					TBILI	DBILI
					CKMB	CK		cTnI	
	ALB	TIBC	PREALB	FER			FE		
	TP	IgA							
	Transferrin	IgG							
		IgM							
	HBA1c	CHOL				TRIG			
		HDL							
		LDL							
		FT4	FSH	LH		TSH			
		DHEAS	TEST	SHBG		COR			
		PROL		PSA		E2			

Marked individuality in homeostatic set points limits use of population reference intervals.

Use of population reference intervals appropriate for these tests.

RCV = $=2.77 \times \sqrt{(CVa^2 + CVi^2)}$

RCV Physician Summary Table

Real Change Value (RCV)

When monitoring treatment or looking for disease progression, a significant change in serial results based on both analytical and biological variation is represented by the test's best estimate of RCV (RCV = critical difference between serial results, %).

RCV (%) by Test

5%	10%	15%	25%	30%	70%
	ALB (10%)	POTASSIUM (15%)		CREATININE (31%)	
	TP (11%)			UREA (35%)	
			PHOSPHATE (25%)		
CALCIUM (6%)	MAGNESIUM (12%)				PTH (73%)

MU Summary Table

Measurement Uncertainty (MU)

For specific tests and situations, it may also be valid for several samples taken from a patient over a short time

Test	MU (95%CI)	Test	MU (95%CI)
Albumin	4%	Calcium	3%
Calcium	3%	Albumin	4%
Creatinine <100	20%	Magnesium	5%
Creatinine >150	7%	Potassium	5%
Magnesium	5%	TP	6%
PTH	10%	Phosphate	6%
Phosphate	6%	Creatinine >150	7%
Potassium	5%	Urea	9%
TP	6%	PTH	10%
Urea	9%	Creatinine <100	20%

Calculation of number of samples required

It is easy to calculate the number of samples required to obtain an estimate within a certain percentage of the true individual homeostatic setting point of the individual from the formula based on a simple standard error of the mean estimate [3],

$$n = [Z * [CV_A^2 + CV_I^2]^{1/2}/D]^2$$

where **Z** is the number of standard deviations appropriate to the probability - and 1.96 is very often used since this is the 95% probability [$P < 0.05$] level;
CV_A is the analytical precision at the level of the homeostatic setting point;
CV_I is the within-subject biological variation; and
D is the percentage deviation allowed from the true homeostatic setting point.

Here is an internet calculator to perform this task. You can use this calculator to verify the numbers in the examples below.

Critical Number of Samples Calculator	
Enter the CV_I, CV_A, Deviation **as percentages** to estimate the number of repeat analyses required. You can also enter the Z-value.	
Z-value (Z)	1.96
Analytical CV (CV_A)	
Intra-individual CV (CV_I)	
% Deviation	
Clear	Calculate
Critical Number of Samples (95% confidence):	

https://www.westgard.com/dispersion-calculator-and-critical-number-of-test-samples.htm

So…are we doing the right thing right?

1

For some analytes the current situation of local RIs is not defendable.

2

Great minds have already spent much time on hRIs.

3

The individual patient is being treated, not the population:

We need to promote RCVs as well as hRIs.

Harmonizing Reference Intervals (hRIs) ≠ Result Uncertainty (RU)

What do you think the main concerns will be for harmonized reference intervals in your lab?

How can we do a better job of conveying what a significant change is for a test?

Please write down your current thoughts on these questions!

Summary

The laboratory is responsible for:

- Standardizing and optimizing the pre-analytical, analytical and post-analytical factors that contribute to result interpretation and ultimately optimized patient care.
  - ***Harmonization of reference intervals is an integral part of this!***
  - Understanding Clinicians' assumptions associated with testing and result interpretation.
  - Ensure the testing cycle is "fit for purpose".

Clinicians and patients expect that laboratory results are comparable!

Summary

- **Current practices for reference intervals are not perfect!**
  - Expensive, time-consuming, and difficult to do properly
    age/sex partitions; recruiting and identifying healthy "reference" volunteers
  - Reference intervals only assessed at beginning over 1 or 2 lots of reagents, and 1 (maybe 2) calibrations.
  - Common to correlate with previous method, or use the kit insert reference intervals; or ***modifications*** of these!
- **Bias**
  - Assess and ***monitor over time*** at appropriate concentrations.
  - Affects the ***false positive (FP) or false negative (FN) rates*** associated with a reference interval… ***monitor over time!***

Summary

Harmonization of reference intervals has been advocated for more than 10 years!

- Initiatives at the national levels for Nordic countries, UK, Japan, Australia and New Zealand, United States, Canada…
- Collaborative process involving consensus, comparisons, data mining, and direct determination of national RIs.
- Over 25 analytes have been considered for hRIs.

It is the laboratory's responsibility to understand how results are used (i.e. diagnosis versus monitoring) and to ensure appropriate result interpretation (i.e. RIs and RCVs).

In Summary:

"TO DO" list for your laboratory:

1) *Implement* pediatric hRIs.
2) *Prepare* to implement adult hRIs.
3) *Consider* how to inform your physicians about hRIs and RCV
4) *Review* your ancillary result interpretation information to ensure you are optimizing patient care as much as possible.

Thank you!

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Any questions or comments welcome!