Common Reference Intervals

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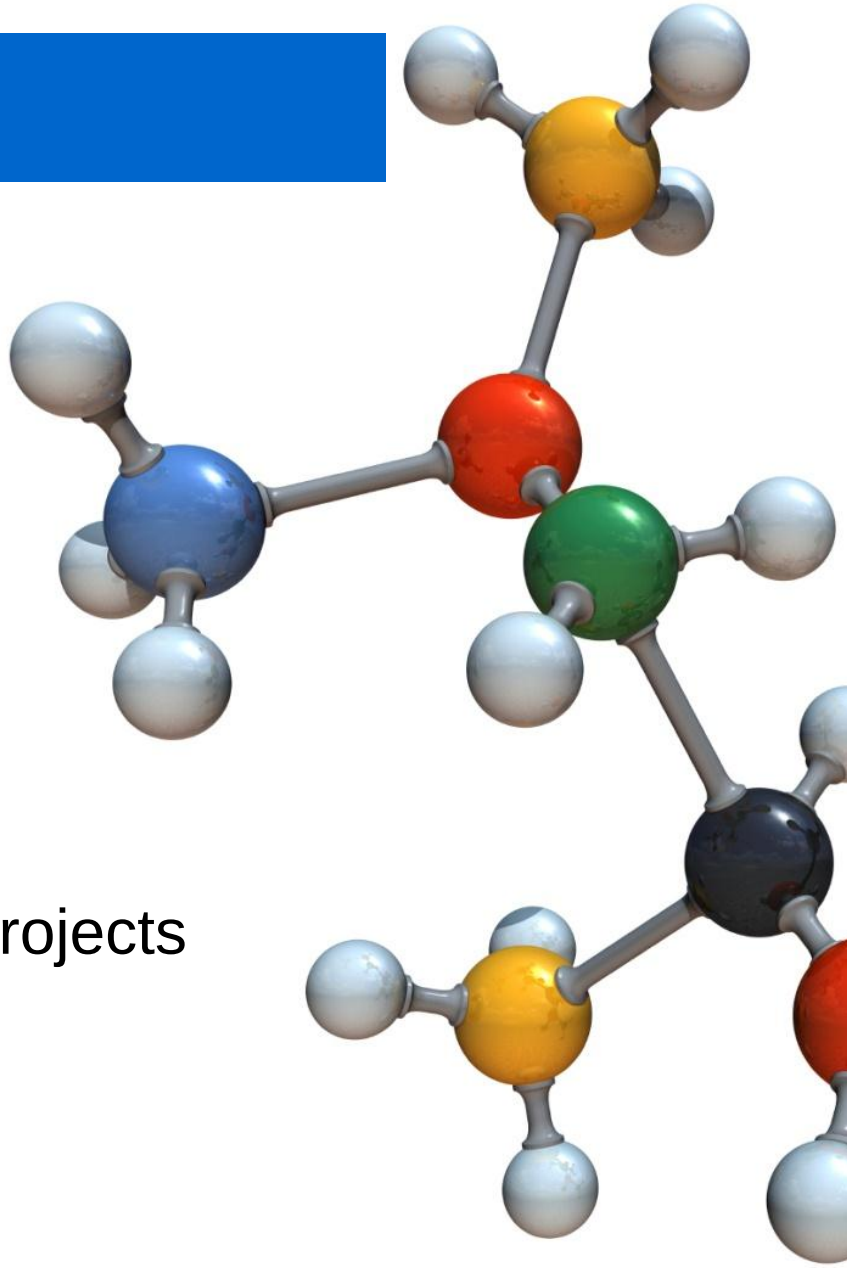
4th Vietnam CPC

14th July 2012

Diagram: AACB Harmonisation logo

Overview

1. Reference Intervals
   - Traditional Development
   - CLSI guidelines
   - Indirect – Bhattacharya
2. Quality Initiatives
   - Post analytical error
   - Stockholm Criteria
   - Harmonisation
3. Common Reference Interval Projects
   - Examples around the world
   - Current Status
4. Summary



Special Acknowledgement

- A number of the slides for this presentation have been provided / adapted from the 2012 Pathology Update presentation on Common Reference Intervals by Dr Ken Sikaris

- I wish to thank Dr Ken for granting the use of the slides for this presentation

Reference Interval (RI)

Normal can have 3 meanings:

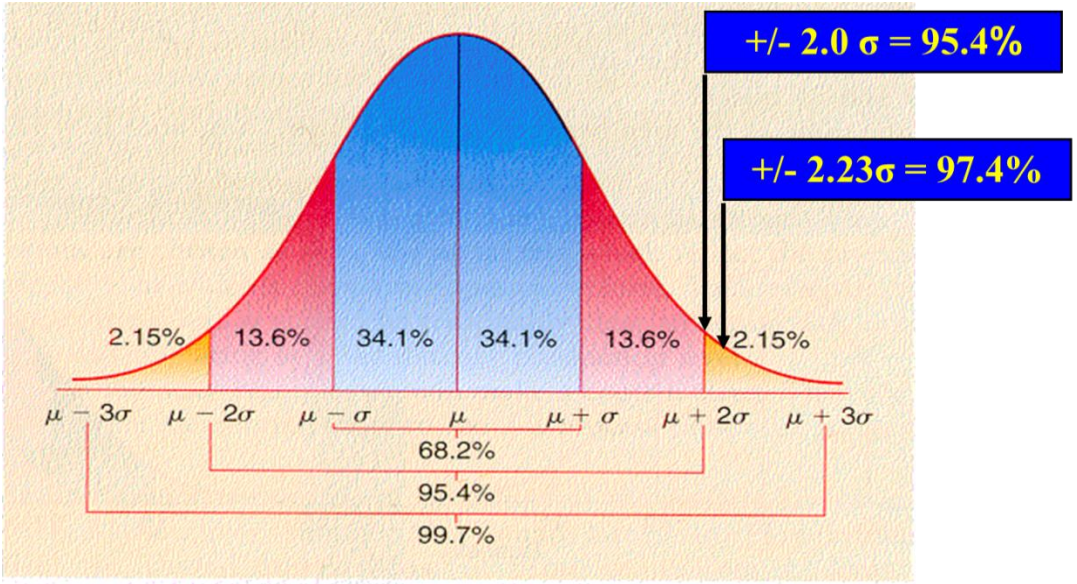
1. Gaussian (mathematical)
2. Common or usual or typical
3. Absence of disease (healthy)

Reference Range (RR) now replaced with term "Reference Interval"

RR ≡ RI

Reference Intervals

- Equivalent to inter-individual biological variation data
- Based on Gaussian Distribution
- Traditionally the central 95% i.e. 2.5 – 97.5, leaves out 5% of population
- Patient results that fall outside the RI are typically flagged in some way as “abnormal”

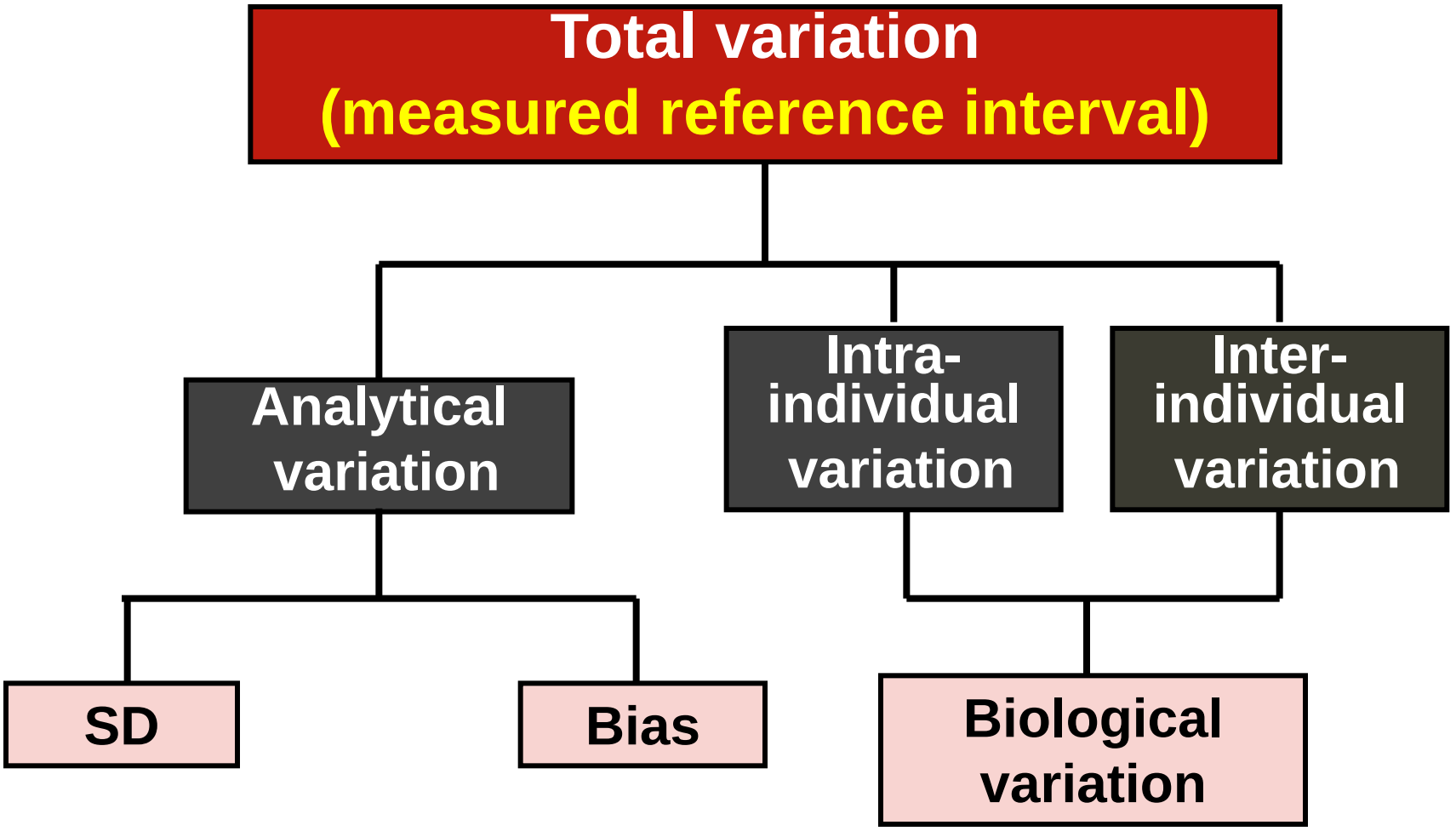


Recommended Ranges: Rather than reference intervals needed because of evidence for clinical outcome

Reference Change Value (RCV):

$= 2^{0.5} \times Z \times (CVa^2 + CVi^2)^{0.5}$

Patient Result Variability



Effects of Biological Variation

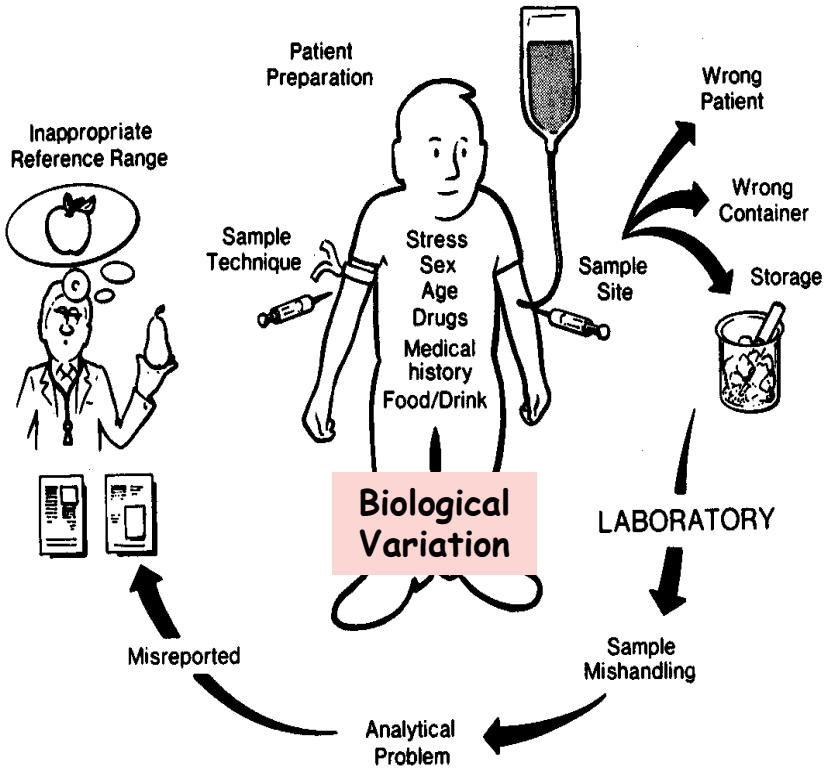


Diagram: From White & Farrance CBR 2004

- Specific ***age*** groups which require consideration
- Possibly in association with ***gender*** :
  - Neonate
  - Child
  - Adolescent
  - Adult
  - Elderly

Biological Variation

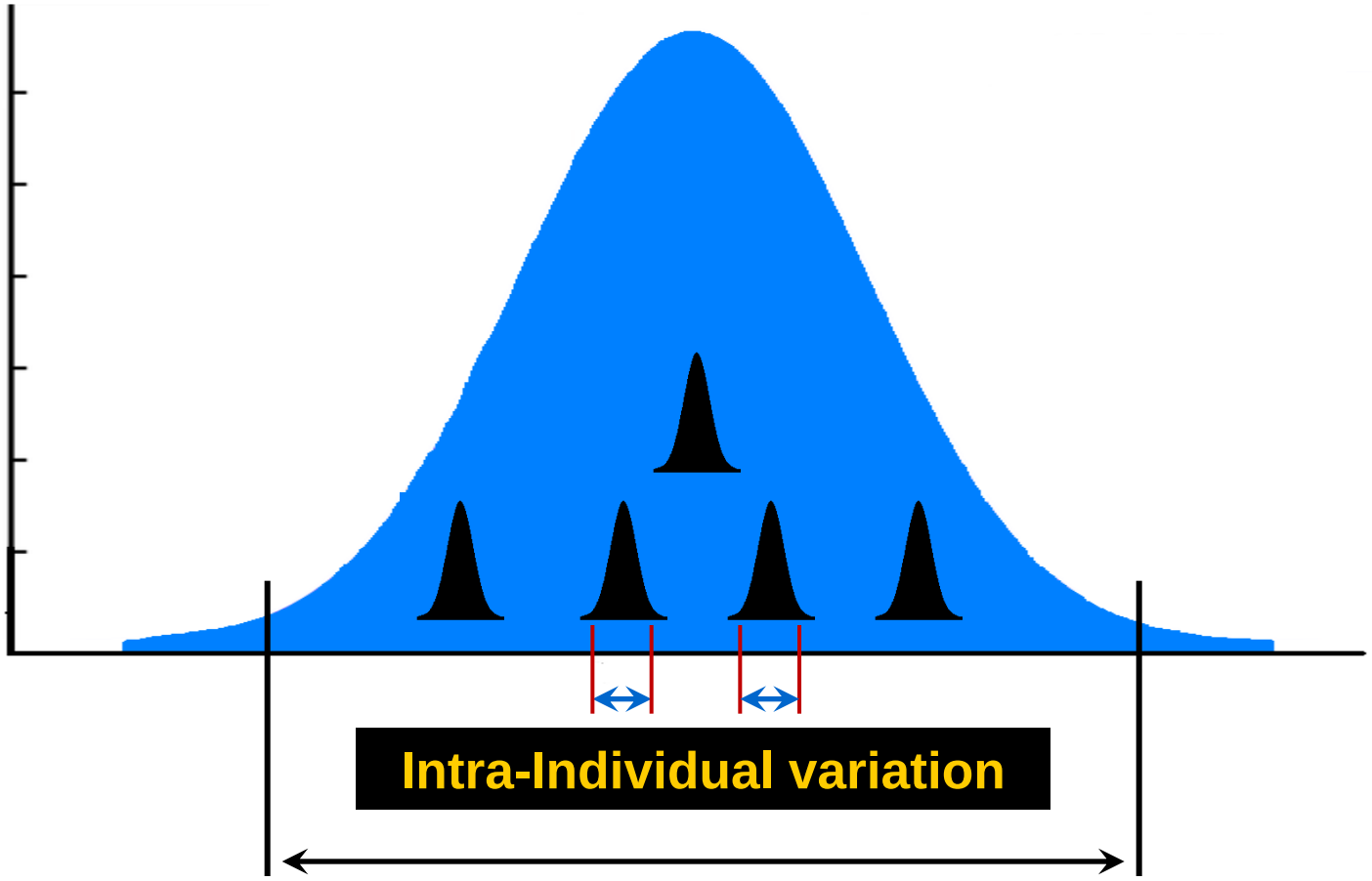
Outside Individual Control

- Age
- Gender
  - Estrogens
  - Androgens
- Body mass (body size)
- Genetic factors
- Physiological factors
  - stage in menstrual cycle
  - stage in pregnancy
  - menopause
- Diurnal factors, circadian rhythm
  - cortisol

Within Individual Control

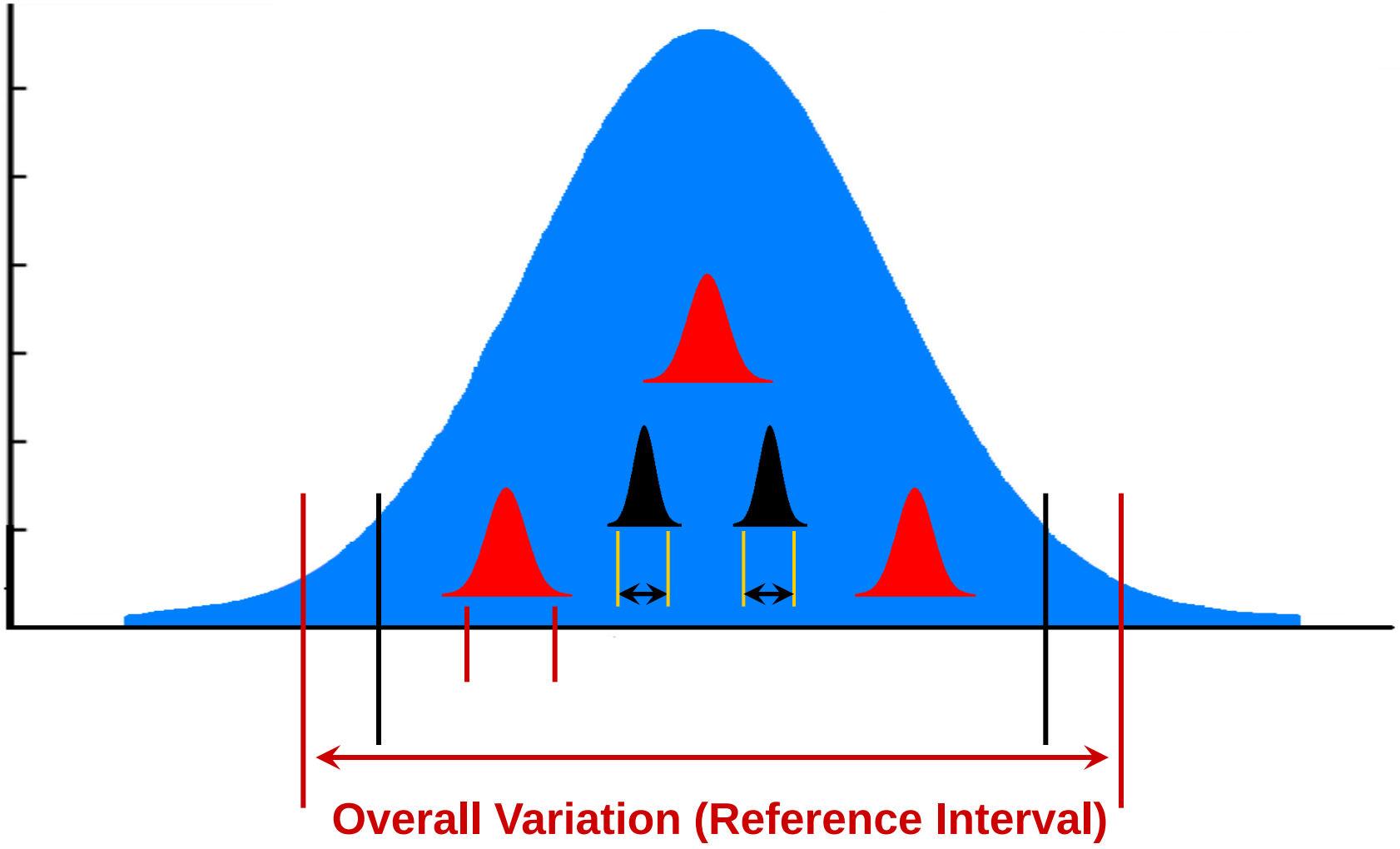
- Diet
  - fasting, time of meals, (glucose, lipids, phosphate)
- Drugs
  - anti-epileptic's, oral contraceptive, (prescription)
  - Vitamin C, caffeine, ethanol, smoking, (non-prescription)
- Posture
  - standing or recumbent, haemoconcentration of 10% to 15% (proteins & bound substances)
- Exercise (lactate, GH)
- Mental state (stress, student exams)
- Tourniquet (haemoconcentration)

Biological Variation
Components of Variability

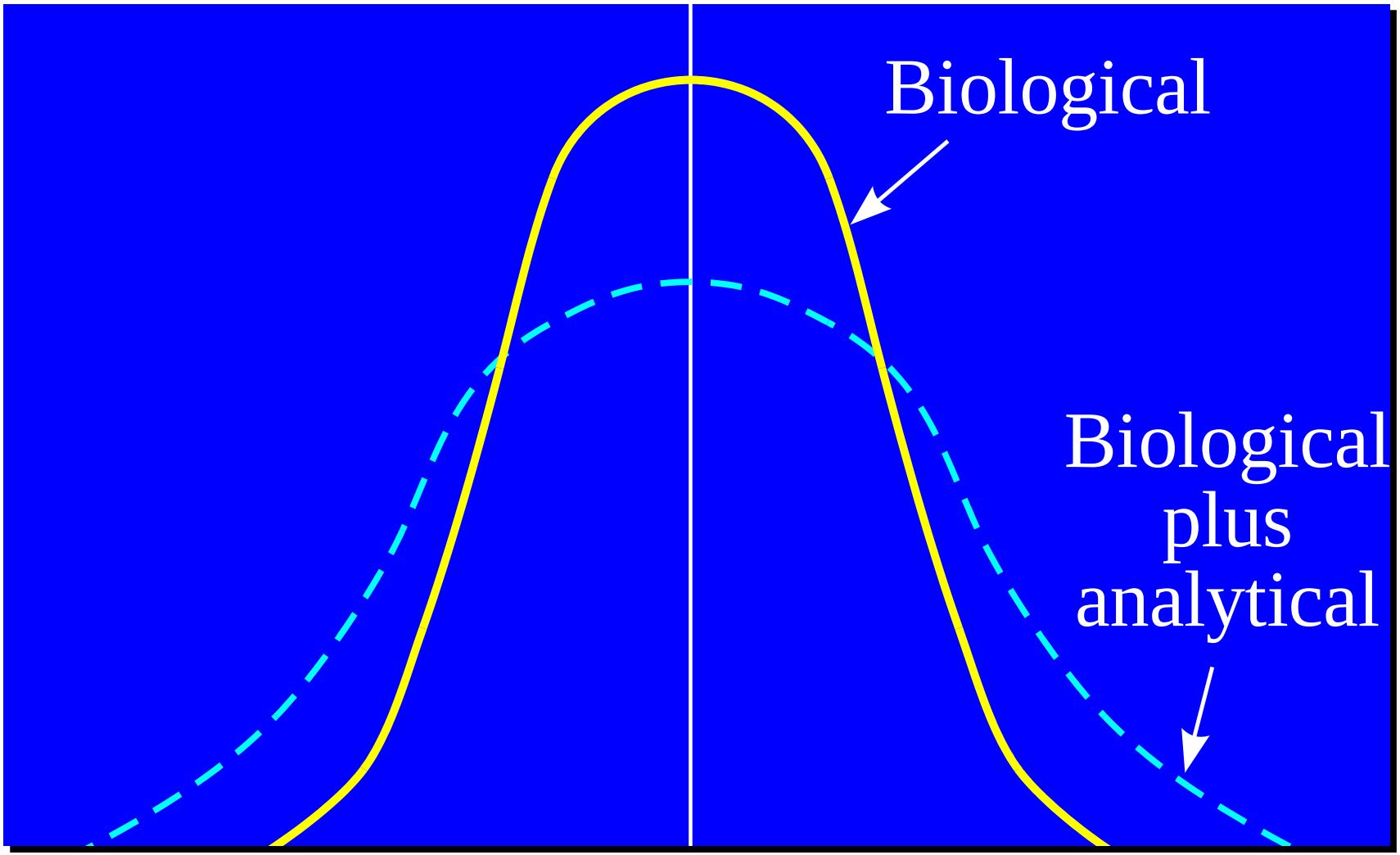


Overall Biological Variation

Reference Interval
Components of Variability



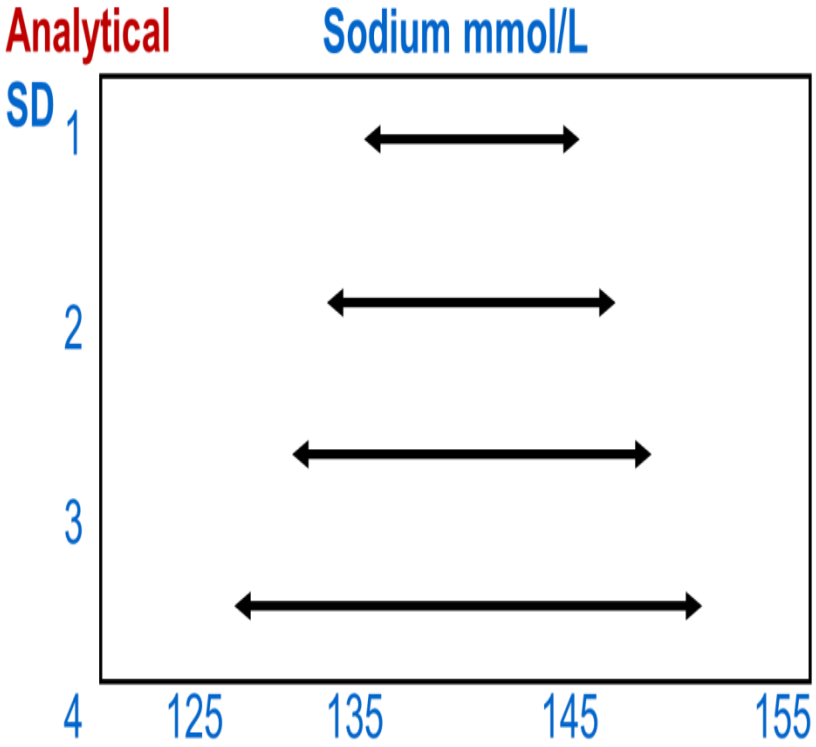
Patient Result Variation



Effect of Analytical Imprecision on Reference Interval

Plasma Sodium mmol/L

Biological SD	Analytical SD	Total SD	Reference Interval
3.0	1.0	3.2	135 - 147
3.0	2.0	3.6	134 - 148
3.0	3.0	4.2	133 - 149
3.0	4.0	5.0	131 - 151



$$\text{Total SD} = \sqrt{(SD_{biol}^2 + SD_{anal}^2)}$$

Biological Variation Data

Section of the Biological Variation database:

- First presented at Stockholm International Consensus Conference on Strategies to Set Global Analytical Quality Specifications in Laboratory Medicine
- Scan J Clin Lab Invest 1999;59:475-586
- 2012: 7th edition comprising >320 analytes

		Biological Variation		Desirable specification		
	Analyte	CVw	CVg	I(%)	B(%)	TE(%)
S-	Calcium	1.9	2.8	1	0.8	2.4
U-	Calcium, ionized	1.7	2.2	0.9	0.7	2.1
S-	Chloride	1.2	1.5	0.6	0.5	1.5
S-	Cholesterol	5.4	15.2	2.7	4	8.5
S-	**Creatinine**	**5.3**	**14.2**	**2.7**	**3.8**	**8.2**
S-	Glucose	5.7	6.9	2.9	2.2	6.9
B-	Hematocrit	2.8	6.4	1.4	1.7	4.1
B-	Hemoglobin	2.8	6.6	1.4	1.8	4.1
B-	Hemoglobin A1 C	3.4	5.1	1.7	1.5	4.3
S-	HDL cholesterol	7.1	19.7	3.6	5.2	11.1
B-	Lactate	27.2	16.7	13.6	8	30.4
B-	pCO2	4.8	5.3	2.4	1.8	5.7
B-	pH [H+]	3.5	2	1.8	1	3.9
B-	pH (pH units)	0.2	---	0.1	---	---
S-	Potassium	4.8	5.6	2.4	1.8	5.8
P-	Prothrombin time	4	6.8	2	2	5.3
(B)Erythr-	Sodium	1.8	12.4	0.9	3.1	4.6
S-	Sodium	0.7	1	0.4	0.3	0.9
S-	Triglyceride	20.9	37.2	10.5	10.7	27.9

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

Developing Reference Intervals

Sample Size

The IFCC & CLSI protocols typically suggest a minimum of 120 reference individuals for each sample or subgroup

Population

A set of selection criteria is required, which determines who should be included or excluded from the group of reference individuals

Partition Criteria (gender, age, fasting, etc ..) usually required

Possible Exclusion Criteria

- Risk factors
  - obesity
  - hypertension
  - genetically determined risk
- Specific physiological states
  - pregnancy
  - excessive exercise
- Disease
- Intake of pharmacologically active agents
  - drug treatment for disease
  - oral contraceptives
  - alcohol, nicotine

Defining the Reference Interval

Direct Approach

1. Kit Inserts
2. Publications / Textbooks
3. Historical 'in house' studies
   - Guideline compliant studies (eg CLSI C28:A3)
   - Pre-guideline studies
   - Pre-historic studies

Indirect Approach

4. Bhattacharya
   - Assume that significant subset of laboratory results are from 'unaffected' patients
   - Use statistical means to derive the 'healthy' subpopulation
     - 'disease affected' v.s. 'unaffected'

Common Sources for the "Direct Approach" if new RI required

Kit Insert

- Development of RI is resource intensive
- Now far more dependent on manufacturers to establish scientifically sound RI
- All kit inserts generally state that the RI should be verified by the lab
- This is less labour intensive by doing:
  - Patient comparisons old & new method
  - Transference of RI

Published Data

- Published RI studies are often used my manufacturers for their kit inserts
- Journal or Text books
- Also useful for specific population groups
- May be method specific
- These published RI should be verified by the lab
- Can use:
  - Transference of RI

CLSI Compliant RI Studies

- CLSI / IFCC
  C28-A3
  November 2008
  - Published
  - In-house (unpublished)

Transference of RI: Comparing the Analytical Systems

1. Appropriateness of donor reference laboratories RI
2. Comparability of pre-analytical factors
3. Comparability of analytical method: i.e. Assay results are highly correlated but there is a proportional bias e.g.

$y = 1.50\ x - 0.832,\ r^2 = 0.990$

A result of 100 by the old method will now be 149 with the new method
A result of 500 by the old method will now be 749 with the new method

4. Comparability of test subjects
5. Validation

Validating the Transference of RI

CLSI Section 11

11 Validation

Essentially, three approaches can be used to assess the acceptability of the transference of a reference interval:

(1) a subjective assessment;
(2) a statistical test on a relatively small number of reference individuals (eg, $n = 20$); and
(3) an evaluation of a larger number of reference individuals (but fewer than $n = 120$, the number needed to perform a standard reference interval study).

11.1 Validation: Subjective

The acceptability of the transfer may be rather subjectively assessed by a careful inspection of the pertinent factors of the original appropriate reference value study. To be able to do this, all of the reference population demographic variables and geographic locations must be adequately described and be available for review. Also, the preanalytical and the analytical procedural details, analytical performance, the complete set of reference values, and the method of estimating the reference interval must be stated. If, in the judgment of the laboratorian, these factors are consistent with the receiving laboratory's operation and test subject population, then the reference interval may be transferred without a requirement for any receiving laboratory validation studies, other than a documentation of these considerations.

Transference of RI: Comparing the Test Subject Populations

CLSI section 11.2

11.2 Validation: Using Small Numbers of Reference Individuals

This approach, calling for the receiving laboratory to test 20 selected subjects using the comparable or same method of analysis, and accepting the manufacturer's or donor laboratory's limits if two or fewer test results fall outside those limits, is statistically sound, as may be proven by recourse to tables of the binomial distribution.

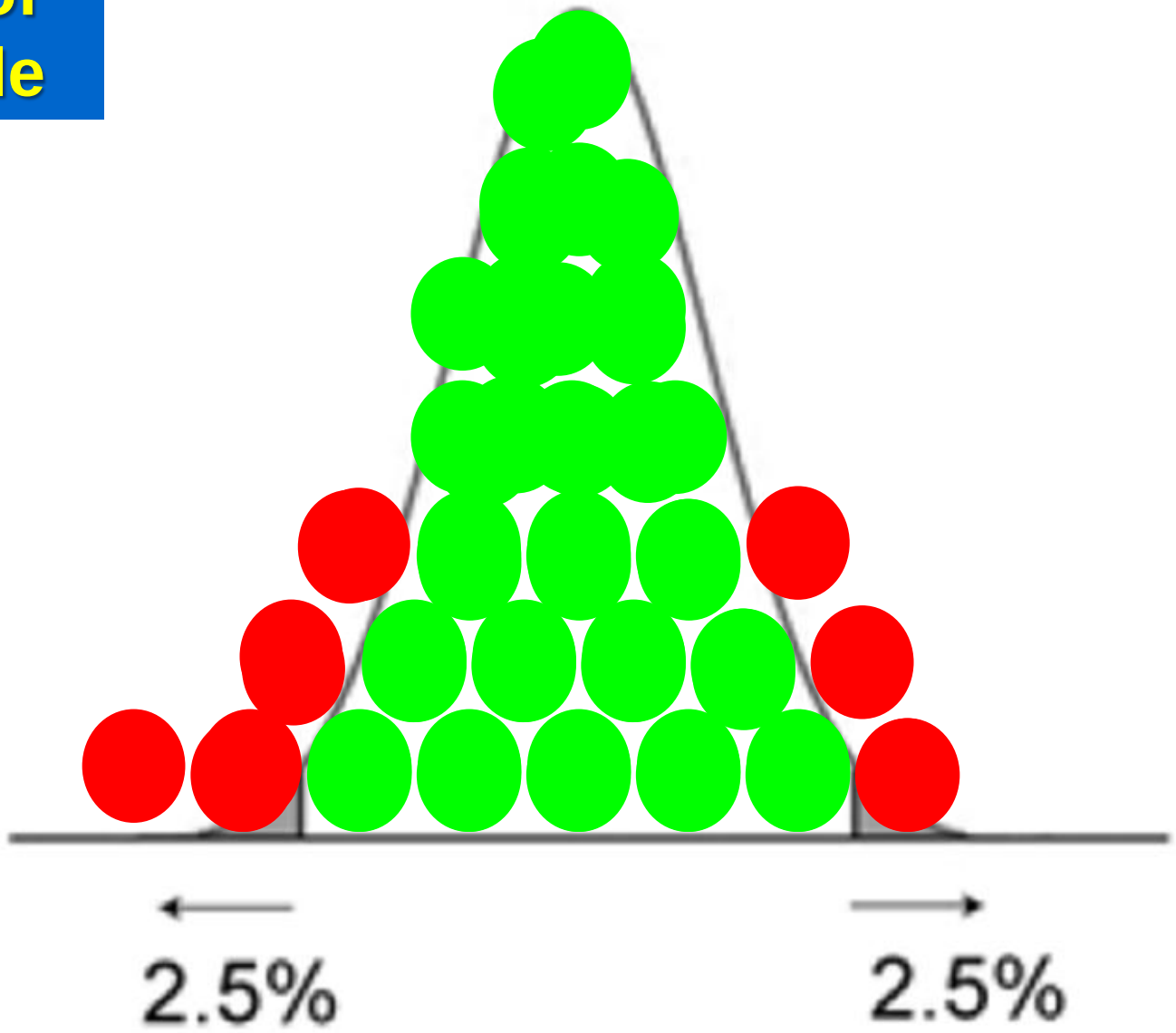
N=20

18 or more must fall into reference interval

- This approach works if the RI applied is suitably narrow (i.e. imprecision is comparable
- Also needs the same accuracy base
- Decreased Imprecision a problem with this approach
  - Reduce Cvi - Eg Collection/Transport
  - Reduce Cva - Eg Within run

Limitations of the 18/20 Rule

1. Recognises inaccuracy
2. Recognises increased imprecision
3. Does **NOT** recognise decreased imprecision



Indirect: “Bhattacharya” Reference Intervals

A SIMPLE METHOD OF RESOLUTION OF A DISTRIBUTION INTO GAUSSIAN COMPONENTS

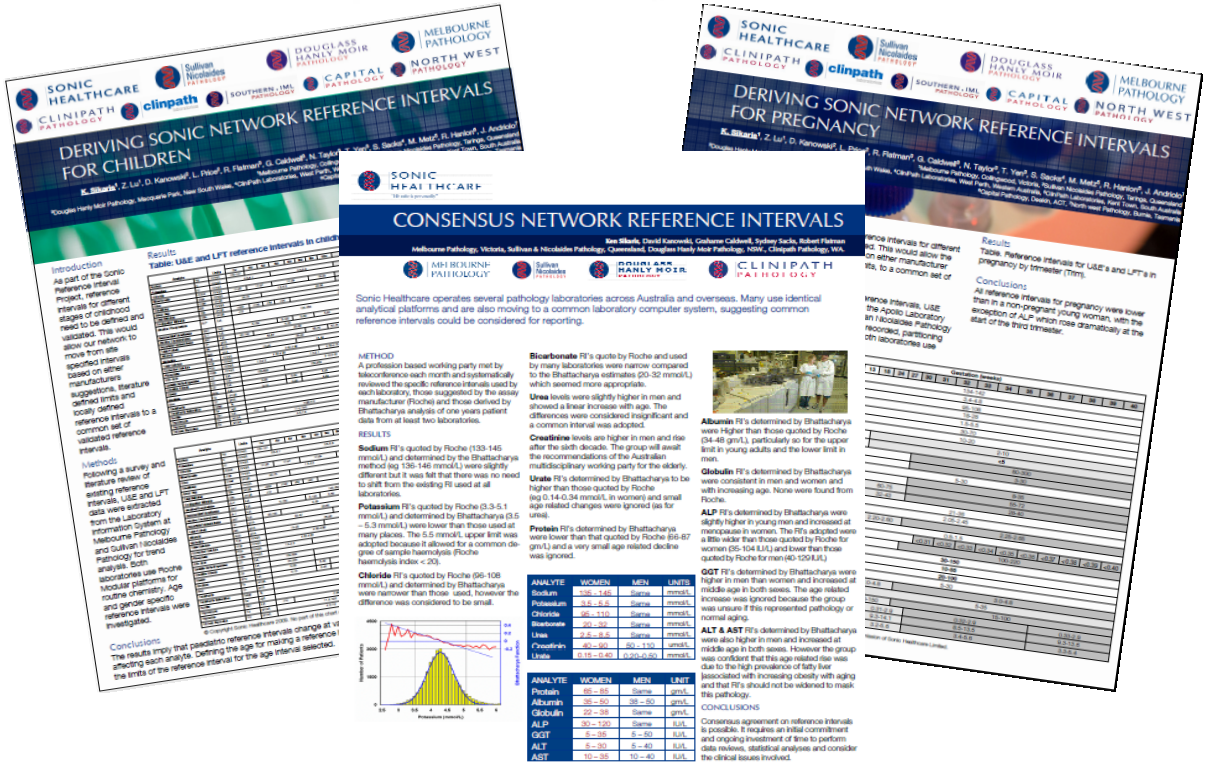
C. G. BHATTACHARYA

Central Inland Fisheries Research Institute, Barrackpore, India[1]

SUMMARY

An approximate method of solution is given of the problem of resolution of a distribution into Gaussian components when the component distributions are adequately separated. Illustrative examples are given.

- Data mining
- Ideal for large labs
- Predominantly an OP population
- Sonic in Australia have done this
- Outcome = Harmonised RI



Arzideh F et al, J Lab Med 2009;33:52-66

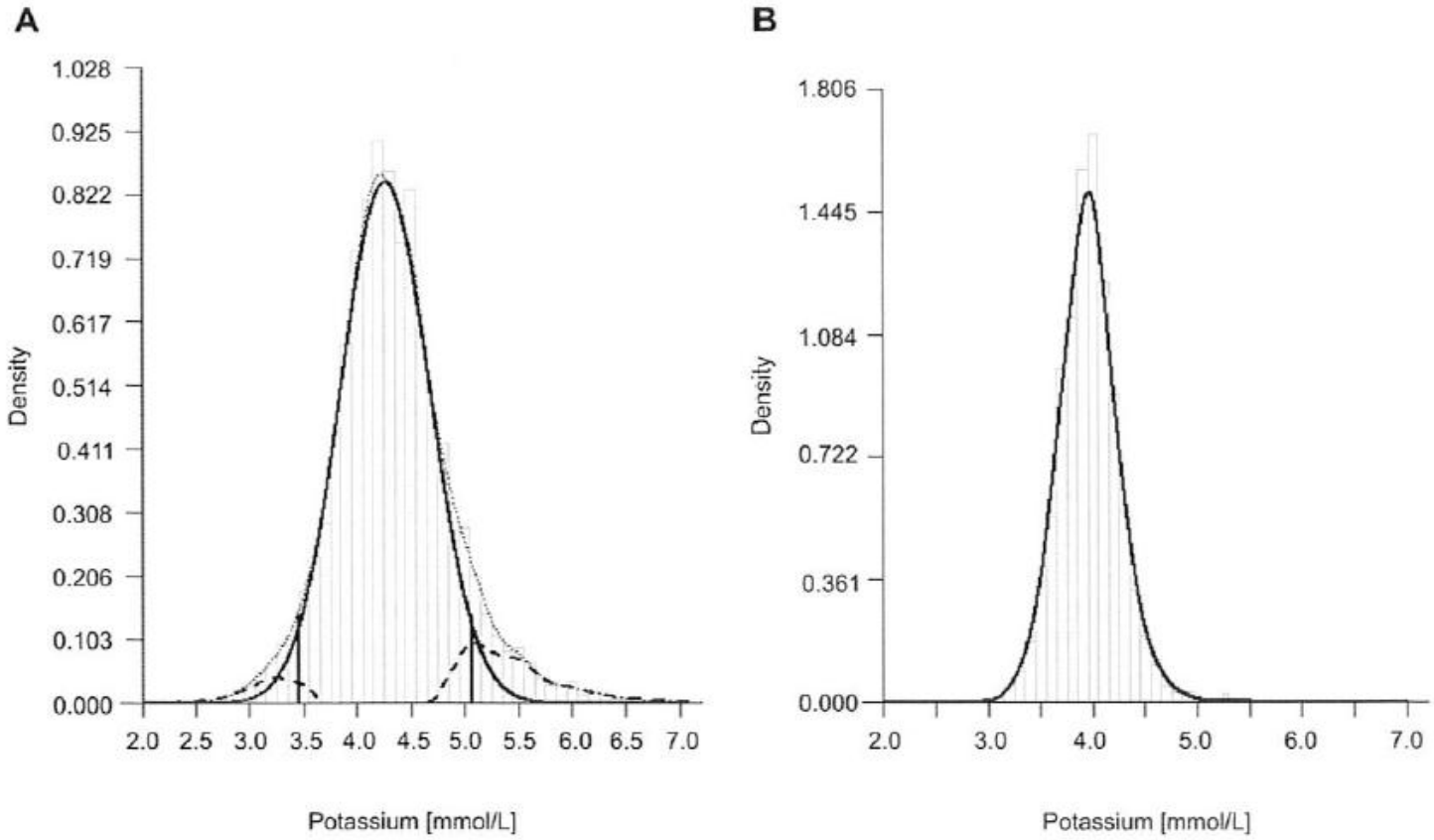
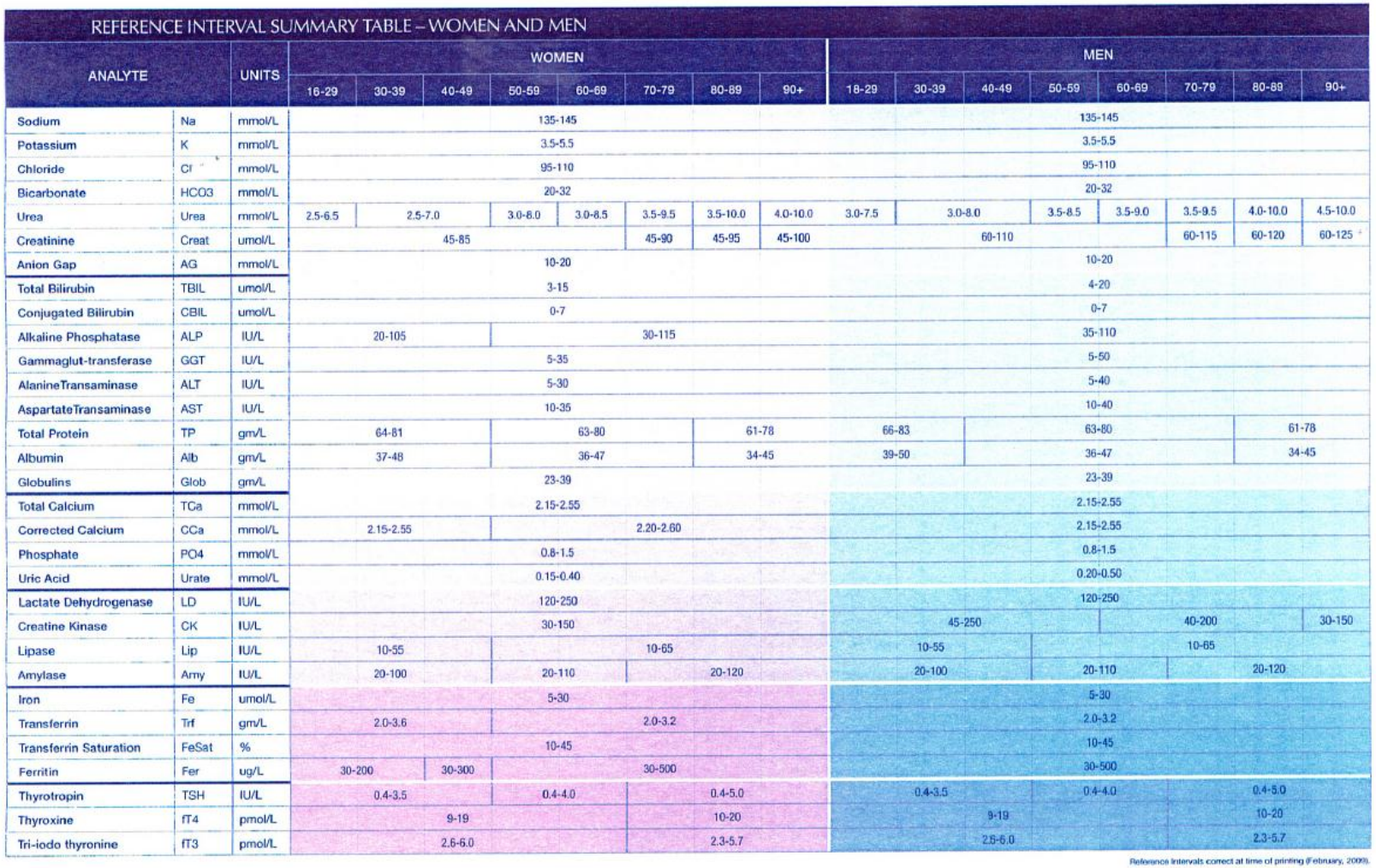


Figure 1 Distribution of serum potassium concentrations (A) from patients (laboratory H, n = 13291) and (B) from blood donors (laboratory B, n = 1129). Solid curves display the estimated distributions of the non-diseased subpopulations, dashed curves of the diseased and dotted curves of the mixed population. Perpendicular solid lines represent $RL_{2.5}$ (3.46 mmol/L) and $RL_{97.5}$ (5.08 mmol/L).

Adapted from slide by Dr Ken

Sonic "Bhattacharya" Adult RI



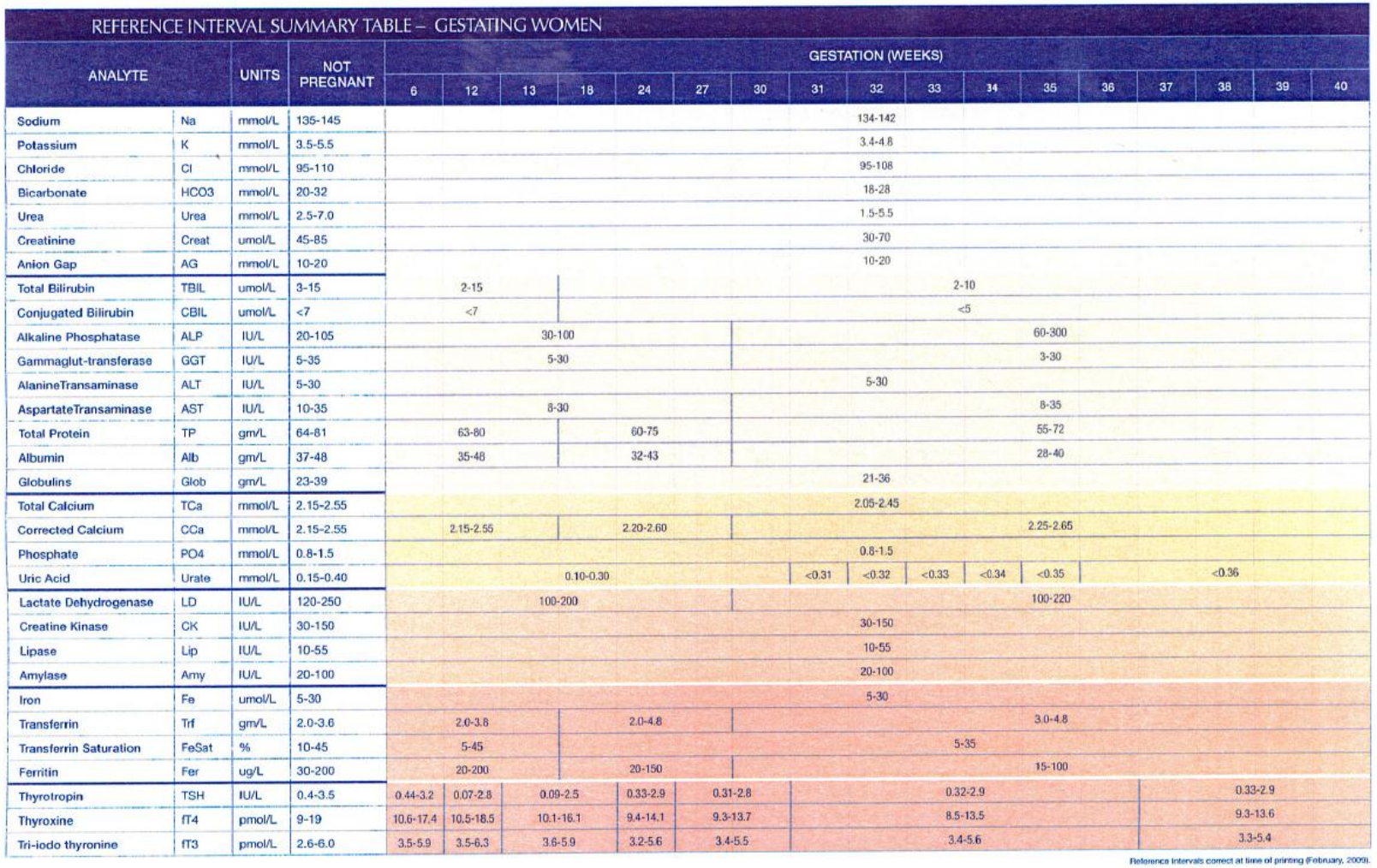
REFERENCE INTERVAL SUMMARY TABLE – WOMEN AND MEN

ANALYTE		UNITS	WOMEN								MEN							
			16-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	18-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Sodium	Na	mmol/L	135-145								135-145							
Potassium	K	mmol/L	3.5-5.5								3.5-5.5							
Chloride	Cl	mmol/L	95-110								95-110							
Bicarbonate	HCO3	mmol/L	20-32								20-32							
Urea	Urea	mmol/L	2.5-6.5	2.5-7.0		3.0-8.0	3.0-8.5	3.5-9.5	3.5-10.0	4.0-10.0	3.0-7.5	3.0-8.0		3.5-8.5	3.5-9.0	3.5-9.5	4.0-10.0	4.5-10.0
Creatinine	Creat	umol/L	45-85					45-90	45-95	45-100	60-110					60-115	60-120	60-125
Anion Gap	AG	mmol/L	10-20								10-20							
Total Bilirubin	TBIL	umol/L	3-15								4-20							
Conjugated Bilirubin	CBIL	umol/L	0-7								0-7							
Alkaline Phosphatase	ALP	IU/L	20-105			30-115					35-110							
Gammaglut-transferase	GGT	IU/L	5-35								5-50							
AlanineTransaminase	ALT	IU/L	5-30								5-40							
AspartateTransaminase	AST	IU/L	10-35								10-40							
Total Protein	TP	gm/L	64-81			63-80			61-78		66-83		63-80				61-78	
Albumin	Alb	gm/L	37-48			36-47			34-45		39-50		36-47				34-45	
Globulins	Glob	gm/L	23-39								23-39							
Total Calcium	TCa	mmol/L	2.15-2.55								2.15-2.55							
Corrected Calcium	CCa	mmol/L	2.15-2.55			2.20-2.60					2.15-2.55							
Phosphate	PO4	mmol/L	0.8-1.5								0.8-1.5							
Uric Acid	Urate	mmol/L	0.15-0.40								0.20-0.50							
Lactate Dehydrogenase	LD	IU/L	120-250								120-250							
Creatine Kinase	CK	IU/L	30-150								45-250				40-200			30-150
Lipase	Lip	IU/L	10-55			10-65					10-55				10-65			
Amylase	Amy	IU/L	20-100			20-110			20-120		20-100			20-110			20-120	
Iron	Fe	umol/L	5-30								5-30							
Transferrin	Trf	gm/L	2.0-3.6			2.0-3.2					2.0-3.2							
Transferrin Saturation	FeSat	%	10-45								10-45							
Ferritin	Fer	ug/L	30-200		30-300			30-500			30-500							
Thyrotropin	TSH	IU/L	0.4-3.5			0.4-4.0			0.4-5.0		0.4-3.5			0.4-4.0			0.4-5.0	
Thyroxine	fT4	pmol/L	9-19						10-20		9-19						10-20	
Tri-iodo thyronine	fT3	pmol/L	2.6-6.0						2.3-5.7		2.6-6.0						2.3-5.7	

Reference intervals correct at time of printing (February, 2009).

Adapted from slide by Dr Ken

Sonic "Bhattacharya" Pregnancy RI



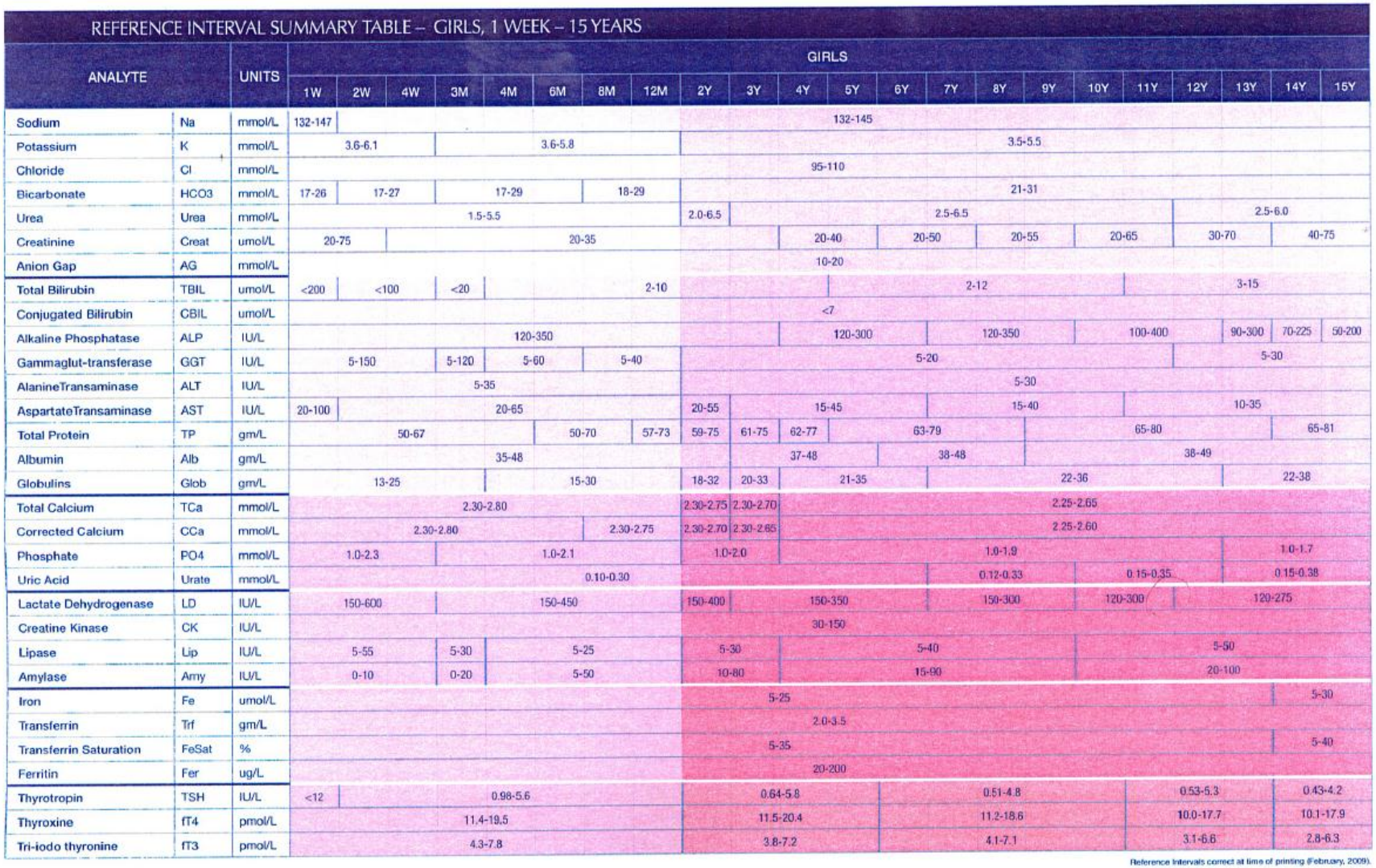
REFERENCE INTERVAL SUMMARY TABLE – GESTATING WOMEN

ANALYTE		UNITS	NOT PREGNANT	GESTATION (WEEKS) 6	12	13	18	24	27	30	31	32	33	34	35	36	37	38	39	40
Sodium	Na	mmol/L	135-145	134-142																
Potassium	K	mmol/L	3.5-5.5	3.4-4.8																
Chloride	Cl	mmol/L	95-110	95-108																
Bicarbonate	HCO3	mmol/L	20-32	18-28																
Urea	Urea	mmol/L	2.5-7.0	1.5-5.5																
Creatinine	Creat	umol/L	45-85	30-70																
Anion Gap	AG	mmol/L	10-20	10-20																
Total Bilirubin	TBIL	umol/L	3-15	2-15								2-10								
Conjugated Bilirubin	CBIL	umol/L	<7	<7								<5								
Alkaline Phosphatase	ALP	IU/L	20-105	30-100											60-300					
Gammaglut-transferase	GGT	IU/L	5-35	5-30											3-30					
AlanineTransaminase	ALT	IU/L	5-30	5-30																
AspartateTransaminase	AST	IU/L	10-35	8-30											8-35					
Total Protein	TP	gm/L	64-81	63-80				60-75							55-72					
Albumin	Alb	gm/L	37-48	35-48				32-43							28-40					
Globulins	Glob	gm/L	23-39	21-36																
Total Calcium	TCa	mmol/L	2.15-2.55	2.05-2.45																
Corrected Calcium	CCa	mmol/L	2.15-2.55	2.15-2.55				2.20-2.60							2.25-2.65					
Phosphate	PO4	mmol/L	0.8-1.5	0.8-1.5																
Uric Acid	Urate	mmol/L	0.15-0.40	0.10-0.30							<0.31	<0.32	<0.33	<0.34	<0.35	<0.36				
Lactate Dehydrogenase	LD	IU/L	120-250	100-200											100-220					
Creatine Kinase	CK	IU/L	30-150	30-150																
Lipase	Lip	IU/L	10-55	10-55																
Amylase	Amy	IU/L	20-100	20-100																
Iron	Fe	umol/L	5-30	5-30																
Transferrin	Trf	gm/L	2.0-3.6	2.0-3.8				2.0-4.8							3.0-4.8					
Transferrin Saturation	FeSat	%	10-45	5-45									5-35							
Ferritin	Fer	ug/L	30-200	20-200				20-150							15-100					
Thyrotropin	TSH	IU/L	0.4-3.5	0.44-3.2	0.07-2.8	0.09-2.5		0.33-2.9	0.31-2.8			0.32-2.9					0.33-2.9			
Thyroxine	fT4	pmol/L	9-19	10.6-17.4	10.5-18.5	10.1-16.1		9.4-14.1	9.3-13.7			8.5-13.5					9.3-13.6			
Tri-iodo thyronine	fT3	pmol/L	2.6-6.0	3.5-5.9	3.5-6.3	3.6-5.9		3.2-5.6	3.4-5.5			3.4-5.6					3.3-5.4			

Reference intervals correct at time of printing (February, 2009).

Adapted from slide by Dr Ken

Sonic "Bhattacharya" Paediatric Girl RI



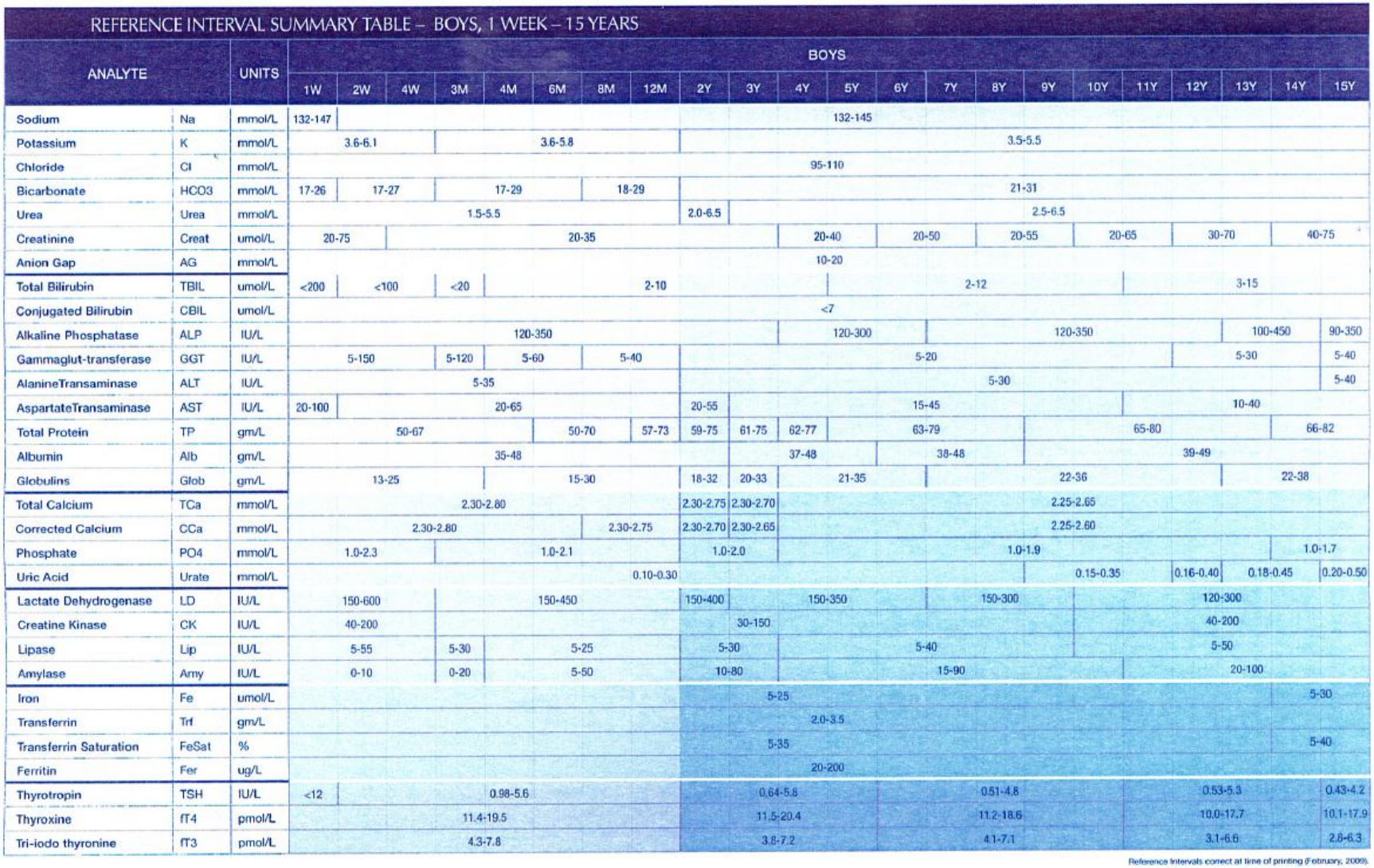
REFERENCE INTERVAL SUMMARY TABLE – GIRLS, 1 WEEK – 15 YEARS

ANALYTE		UNITS	GIRLS																				
			1W	2W	4W	3M	4M	6M	8M	12M	2Y	3Y	4Y	5Y	6Y	7Y	8Y	9Y	10Y	11Y	12Y	13Y	14Y	15Y
Sodium	Na	mmol/L	132-147								132-145													
Potassium	K	mmol/L		3.6-6.1				3.6-5.8									3.5-5.5							
Chloride	Cl	mmol/L											95-110											
Bicarbonate	HCO3	mmol/L	17-26		17-27			17-29		18-29							21-31							
Urea	Urea	mmol/L					1.5-5.5				2.0-6.5				2.5-6.5							2.5-6.0		
Creatinine	Creat	umol/L		20-75					20-35					20-40		20-50		20-55		20-65		30-70		40-75
Anion Gap	AG	mmol/L												10-20										
Total Bilirubin	TBIL	umol/L	<200		<100		<20			2-10					2-12						3-15			
Conjugated Bilirubin	CBIL	umol/L												<7										
Alkaline Phosphatase	ALP	IU/L						120-350						120-300		120-350			100-400			90-300	70-225	50-200
Gammaglut-transferase	GGT	IU/L		5-150			5-120	5-60		5-40					5-20						5-30			
AlanineTransaminase	ALT	IU/L						5-35										5-30						
AspartateTransaminase	AST	IU/L	20-100					20-65			20-55			15-45			15-40				10-35			
Total Protein	TP	gm/L				50-67			50-70	57-73	59-75	61-75	62-77		63-79				65-80				65-81	
Albumin	Alb	gm/L						35-48					37-48			38-48				38-49				
Globulins	Glob	gm/L			13-25				15-30		18-32	20-33		21-35				22-36				22-38		
Total Calcium	TCa	mmol/L				2.30-2.80					2.30-2.75	2.30-2.70				2.25-2.65								
Corrected Calcium	CCa	mmol/L				2.30-2.80				2.30-2.75	2.30-2.70	2.30-2.65				2.25-2.60								
Phosphate	PO4	mmol/L		1.0-2.3				1.0-2.1			1.0-2.0						1.0-1.9					1.0-1.7		
Uric Acid	Urate	mmol/L							0.10-0.30								0.12-0.33		0.15-0.35			0.15-0.38		
Lactate Dehydrogenase	LD	IU/L		150-600				150-450			150-400		150-350				150-300		120-300		120-275			
Creatine Kinase	CK	IU/L												30-150										
Lipase	Lip	IU/L		5-55			5-30	5-25			5-30			5-40						5-50				
Amylase	Amy	IU/L		0-10			0-20	5-50			10-80			15-90						20-100				
Iron	Fe	umol/L												5-25										5-30
Transferrin	Trf	gm/L												2.0-3.5										
Transferrin Saturation	FeSat	%												5-35										5-40
Ferritin	Fer	ug/L												20-200										
Thyrotropin	TSH	IU/L	<12					0.98-5.6					0.64-5.8				0.51-4.8				0.53-5.3			0.43-4.2
Thyroxine	fT4	pmol/L						11.4-19.5					11.5-20.4				11.2-18.6				10.0-17.7			10.1-17.9
Tri-iodo thyronine	fT3	pmol/L						4.3-7.8					3.8-7.2				4.1-7.1				3.1-6.6			2.8-6.3

Reference intervals correct at time of printing (February, 2009).

Adapted from slide by Dr Ken

Sonic "Bhattacharya" Paediatric Boy RI



REFERENCE INTERVAL SUMMARY TABLE – BOYS, 1 WEEK – 15 YEARS

ANALYTE		UNITS	BOYS																			
			1W	2W	4W	3M	4M	6M	8M	12M	2Y	3Y	4Y	5Y	6Y	7Y	8Y	9Y	10Y	11Y	12Y	13Y	14Y	15Y
Sodium	Na	mmol/L	132-147											132-145										
Potassium	K	mmol/L		3.6-6.1				3.6-5.8										3.5-5.5						
Chloride	Cl	mmol/L												95-110										
Bicarbonate	HCO3	mmol/L	17-26		17-27			17-29		18-29								21-31						
Urea	Urea	mmol/L						1.5-5.5			2.0-6.5								2.5-6.5					
Creatinine	Creat	umol/L		20-75					20-35					20-40		20-50		20-55		20-65		30-70		40-75
Anion Gap	AG	mmol/L												10-20										
Total Bilirubin	TBIL	umol/L	<200		<100		<20			2-10					2-12							3-15		
Conjugated Bilirubin	CBIL	umol/L												<7										
Alkaline Phosphatase	ALP	IU/L						120-350						120-300				120-350					100-450	90-350
Gammaglut-transferase	GGT	IU/L			5-150		5-120		5-60		5-40							5-20				5-30		5-40
AlanineTransaminase	ALT	IU/L						5-35											5-30					5-40
AspartateTransaminase	AST	IU/L	20-100					20-65			20-55					15-45							10-40	
Total Protein	TP	gm/L				50-67				50-70	57-73	59-75	61-75	62-77		63-79				65-80			66-82	
Albumin	Alb	gm/L						35-48						37-48			38-48				39-49			
Globulins	Glob	gm/L			13-25				15-30			18-32	20-33		21-35				22-36				22-38	
Total Calcium	TCa	mmol/L						2.30-2.80				2.30-2.75	2.30-2.70						2.25-2.65					
Corrected Calcium	CCa	mmol/L				2.30-2.80				2.30-2.75		2.30-2.70	2.30-2.65						2.25-2.60					
Phosphate	PO4	mmol/L			1.0-2.3				1.0-2.1				1.0-2.0					1.0-1.9						1.0-1.7
Uric Acid	Urate	mmol/L								0.10-0.30									0.15-0.35		0.16-0.40	0.18-0.45		0.20-0.50
Lactate Dehydrogenase	LD	IU/L			150-600				150-450			150-400		150-350			150-300					120-300		
Creatine Kinase	CK	IU/L			40-200								30-150									40-200		
Lipase	Lip	IU/L			5-55		5-30		5-25			5-30				5-40						5-50		
Amylase	Amy	IU/L			0-10		0-20		5-50			10-80					15-90					20-100		
Iron	Fe	umol/L											5-25											5-30
Transferrin	Trf	gm/L												2.0-3.5										
Transferrin Saturation	FeSat	%											5-35											5-40
Ferritin	Fer	ug/L												20-200										
Thyrotropin	TSH	IU/L	<12					0.98-5.6					0.64-5.8				0.51-4.8					0.53-5.3		0.43-4.2
Thyroxine	fT4	pmol/L						11.4-19.5					11.5-20.4				11.2-18.6					10.0-17.7		10.1-17.9
Tri-iodo thyronine	fT3	pmol/L						4.3-7.8					3.8-7.2				4.1-7.1					3.1-6.6		2.8-6.3

Reference Intervals correct at time of printing (February, 2009).

Adapted from slide by Dr Ken

GLOBAL QUALITY INITIATIVES: HARMONISATION OF REFERENCE INTERVALS

Striving for improved patient care

Origin of laboratory errors
.....and impact on patient care

pre-analytical

post-analytical

Plebani, 2006

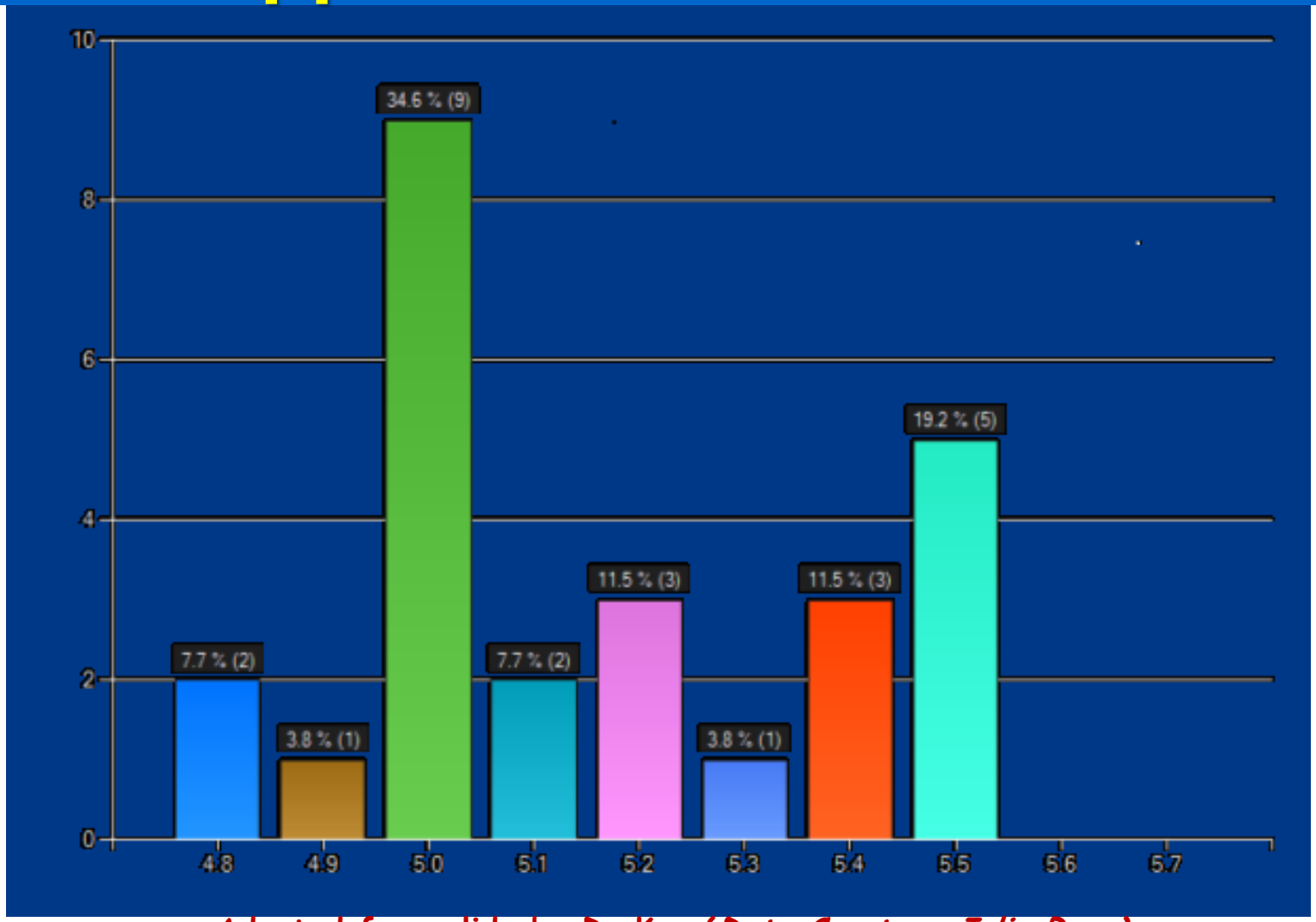
.....so, most 'laboratory errors' occur outside the laboratory

"60-70% of medical decisions based on test results"

Forsman, 1996

Slide from 2010 AACC presentation by Christopher Price and Andrew St John, "Disruptive Innovation: Opportunities and Implications for Laboratory

2011 Australian (AACB) Survey: Upper RI for Potassium



Adapted from slide by Dr Ken (Data Courtesy Julie Ryan)

Arch Pathol Lab Med. 2007;131:348–357

The Origin of Reference Intervals

A College of American Pathologists Q-Probes Study of "Normal Ranges" Used in 163 Clinical Laboratories

Richard C. Friedberg, MD, PhD; Rhona Souers, MS; Elizabeth A. Wagar, MD; Ana K. Stankovic, MD, PhD, MPH; Paul N. Valenstein, MD

Table 2. Source of Reference Intervals*

	Institutions, No. (%)							
	Potassium	Calcium	Magnesium	TSH	Hgb (Male)	Hgb (Female)	Platelets	aPTT
Adult								
Internal study of healthy individuals	70 (44.3)	70 (43.8)	70 (44.6)	75 (48.4)	85 (53.5)	83 (52.5)	81 (51.3)	130 (82.3)
Manufacturer's recommendations/ inserts	55 (34.8)	56 (35.0)	57 (36.3)	46 (29.7)	17 (10.7)	18 (11.4)	19 (12.0)	12 (7.6)
Published literature/ textbooks	19 (12.0)	17 (10.6)	16 (10.2)	12 (7.7)	43 (27.0)	43 (27.2)	44 (27.8)	6 (3.8)
Other laboratories (adopted with internal validation)	8 (5.1)	9 (5.6)	8 (5.1)	10 (6.5)	8 (5.0)	8 (5.1)	8 (5.1)	5 (3.2)
Nonlaboratory medical staff recommendations	2 (1.3)	4 (2.5)	2 (1.3)	4 (2.6)	3 (1.9)	3 (1.9)	3 (1.9)	2 (1.3)
Other laboratories (adopted without internal validation)	0 (0)	0 (0)	0 (0)	2 (1.3)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.3)
Other	4 (2.5)	4 (2.5)	4 (2.5)	6 (3.9)	2 (1.3)	2 (1.3)	2 (1.3)	1 (0.6)

* TSH indicates thyroid-stimulating hormone; Hgb, hemoglobin; and aPTT, activated partial thromboplastin time.

Clin Chem Lab Med 2004;42(7):752–757

Clinical interpretation of reference intervals and reference limits. A plea for assay harmonization

George G. Klee*

If laboratory testing methods could be harmonized, laboratories could potentially share reference data to make these data more reliable.

Harmonisation: (RG definition)

- Is the process of compromise to come to agreement for a common approach
- In the context of laboratory medicine it relates to agreement of processes to provide commonality aimed at improving patient outcome

Rationale

- **Achieving harmonisation and standardisation of clinical assays will provide commutability of results between laboratories**
- **This will produce improved ease of result interpretation for the doctor and patient**
- **Improved clinical care / outcome**

Strategies to Set Global Quality Specifications in Laboratory Medicine

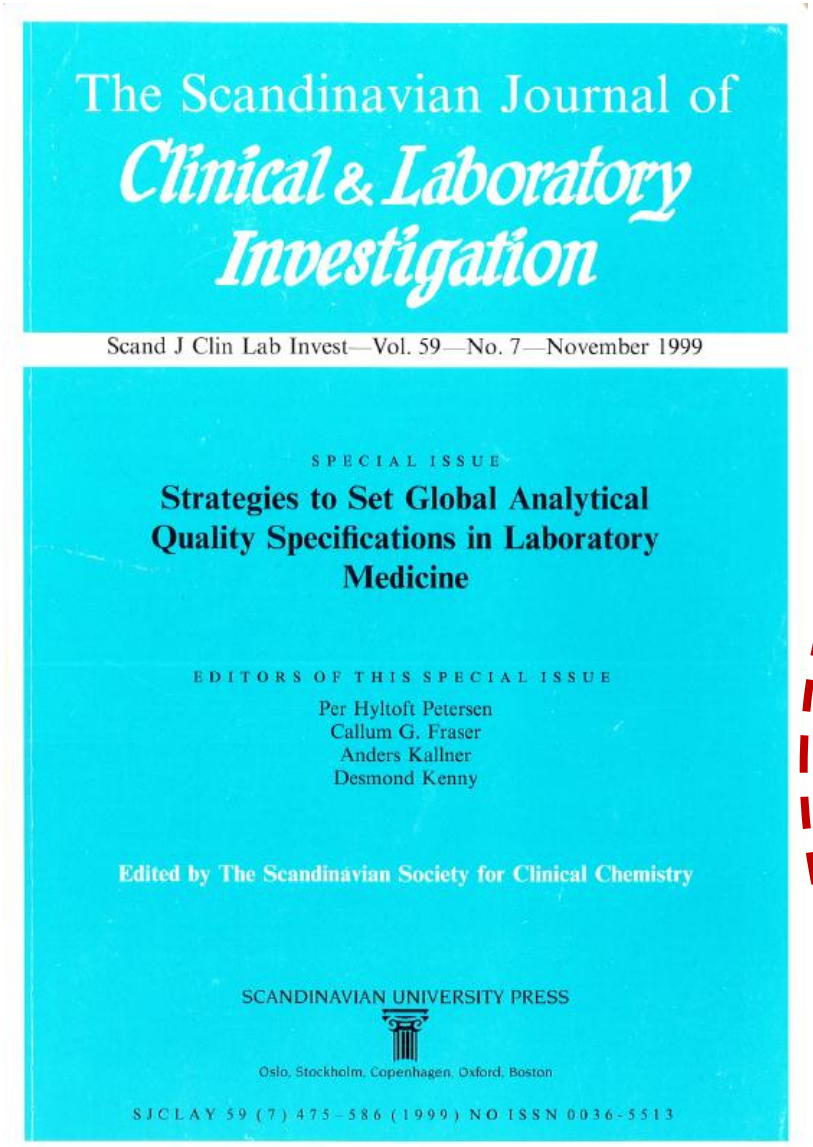
WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

International Union of Pure and Applied Chemistry

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum,
Karolinska Institutet
Stockholm April 24-26, 1999

Adapted from slide by Dr Ken



Consensus agreement

D. KENNY,* C. G. FRASER,† P. HYLTOFT PETERSEN,‡ & A. KALLNER§

*Department of Clinical Biochemistry, Our Lady's Hospital for Sick Children, Dublin, Ireland; †Directorate of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland; ‡Department of Clinical Chemistry, Odense University Hospital, Odense, Denmark; and §Department of Clinical Chemistry, Karolinska Hospital, Stockholm, Sweden

The Editors of this special issue of the *Scandinavian Journal of Clinical and Laboratory Investigation* and the Organising Committee of the Conference: *Strategies to set Global Quality Specifications in Laboratory Medicine*, Stockholm, 24–26 April 1999, are pleased to report that this recent Conference was most successful. Over 100 participants from 27 countries actively contributed to the discussions on the 22 formal presentations. Our primary aim in organizing the Conference was to provide a vehicle for reaching consensus on the setting of global quality specifications in laboratory medicine. This objective was achieved and lively constructive debate after the presentations were completed led to agreement on the principles laid down in the following Consensus Statement.

CONSENSUS STATEMENT*

The main outcome of the Conference was agreement that the following hierarchy of models should be applied to set analytical quality specifications.

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings
2. Evaluation of the effect of analytical performance on clinical decisions in general:
   a. Data based on components of biological variation
   b. Data based on analysis of clinicians' opinions
3. Published professional recommendations
   a. From national and international expert bodies
   b. From expert local groups or individuals
4. Performance goals set by
   a. Regulatory bodies
   b. Organizers of External Quality Assessment (EQA) schemes
5. Goals based on the current state of the art
   a. As demonstrated by data from EQA or Proficiency Testing scheme
   b. As found in current publications on methodology.

Where available, and when appropriate for the intended purpose, models higher in the hierarchy are to be preferred to those at lower levels. The concept of such a hierarchy is described in a recent Editorial in Clinical Chemistry in which the relative merits of the above models are discussed (Clin Chem 1999; 45: 321–3). This hierarchy has also been proposed by the ISO/TC 212/WG 3 subgroup on "Analytical Performance Goals Based on Medical Needs" as the basis for the ongoing revision of ISO/CD 15196. The following matters were also discussed and agreed.

- The above hierarchy includes currently available models; however, new useful concepts will undoubtedly evolve. Implementation of any of the models should use well-defined and described procedures.
- To facilitate the future debate on the setting of analytical quality specifications, there is a need for agreement on concepts, definitions and terms.
- There is a need for continuous improvement in the exchange of information on quality issues: between clinical laboratory professionals and the diagnostics industry, and between clinical laboratory professionals and the users of the laboratory service.

IFCC, IUPAC and WHO kindly sponsored the Conference but it must be noted that the Consensus Statement reflects the views of the presenters and registrants who participated in the Conference and does not necessarily represent those of the sponsoring bodies.

Adapted from slide by Dr Ken

Case for Common Reference Intervals

- What is necessary:
  - Appropriate reference Intervals
  - Evidence exists showing that:
    - Methods are ‘the same’
    - Populations are ‘the same’
  - The quality of common reference intervals depends on the quality of evidence used to derive them
  - i.e. similar to transference of RI

Clin Biochem Rev 2004; 99-104

The Case for Common Reference Intervals

*Graham RD Jones,[1] Antony Barker,[5] Jill Tate,[2] Chen-Fee Lim,[3] Ken Robertson[4]

Table 4. Practical issues with common reference intervals.

1. Organise and support a body to oversee the project.
2. Develop agreed statistical approaches to development and application of common reference intervals.
3. Obtain quality local data for reference intervals.
4. Publish common reference intervals and criteria for use by laboratories.
5. Overcome inertia in laboratories and encourage wide-spread adoption.

Group Initiatives for Harmonisation of Reference Intervals

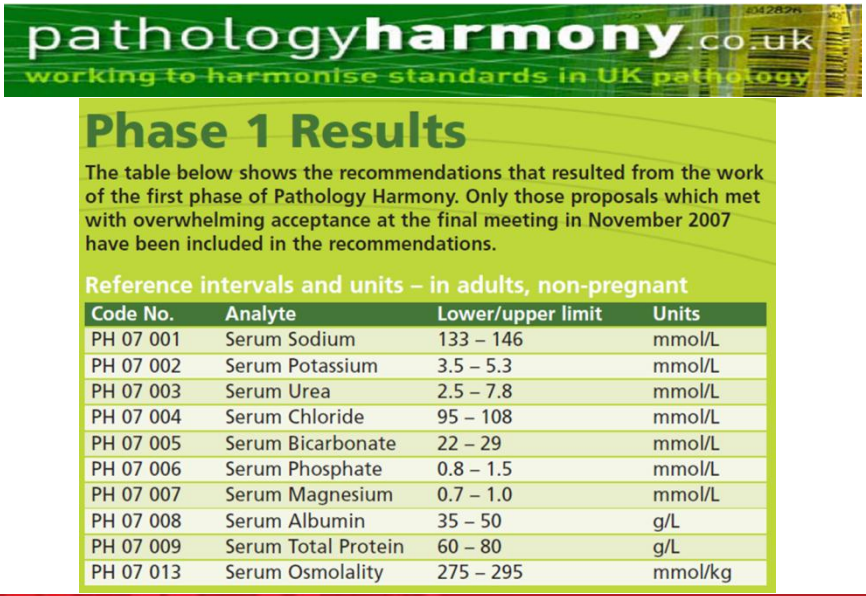
1. ARQAG – Auckland Region Quality Assurance Group – New Zealand
2. SIQAG – Southern Island Quality Assurance Group – New Zealand
3. NORIP – Nordic Reference Interval Project - Scandinavia
4. UKHarmony - UK
5. AACB - Australasia
6. Sonic - Australia
7. Other

Klinisk Biokemi i Norden | 2 | 2003 10

Reference intervals for 25 of the most frequently used properties in clinical chemistry

Proposal by Nordic Reference Interval Project (NORIP)

Pål Rustad (prustad@furst.no), Fürst Medical Laboratory, Oslo



pathologyharmony.co.uk

working to harmonise standards in UK pathology

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

Hierarchy for Reference Intervals

Level	Principle	Reference Limits	Common Interval
1	Clinical Outcome		
2A	Biological variation		
2B	Clinician Survey		
3	Professional Recommendations		
4	Proficiency survey		
5	State of the Art		

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Reference intervals for 25 of the most frequently used properties in clinical chemistry

Proposal by Nordic Reference Interval Project (NORIP)

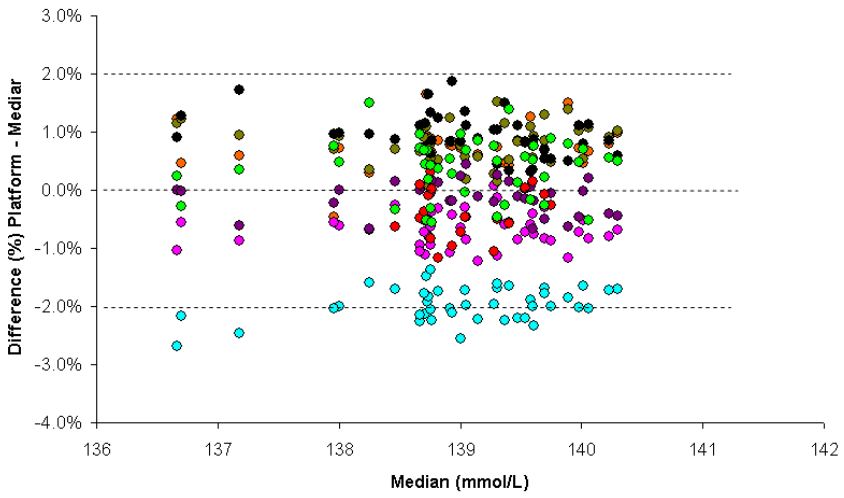
Pål Rustad (prustad@furst.no), Fürst Medical Laboratory, Oslo

Component	Unit	CAL		Quality goal			Calculated					NORIP Reference intervals									
							Serum					Plasma (Li heparin)					Suggestions				
		Target value	Source	Bias	Gender	Age	Low	90% CI	High	90% CI	N	Low	90% CI	High	90% CI	N	Serum Low	Serum High	Plasma Low	Plasma High	Comment
Albumin	g/L	40,52	NTP	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	45.2-45.6	1248			45,4	45.1-45.9	589		45			
						>=70	34,4	33.5-34.8			450	34,5	33.8-34.9			244	34				
Bilirubin	umol/L	8,5	DGKC	6,6 %	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	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 corrected	mmol/L	2,2816		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			=Ca+0.020x(41.3-Alb) where 41.3 g/L
						>=50			2,53	2.52-2.54	1149			2,52	2.49-2.53	558		2,53			is the albumin median
Cholesterol	mmol/L	4,90	NTP	3,0 %	FM	18-29	2,89	2.78-3.04	6,18	6.0-6.37	674	2,95	2.79-3.14	5,89	5.78-6.52	316	2,9	6,1			
						30-49	3,43	3.28-3.55	6,92	6.77-7.19	843	3,35	3.13-3.51	6,75	6.41-7.06	368	3,3	6,9			
						>=50	4,02	3.98-4.14	7,87	7.73-8.09	1216	3,89	3.79-4.01	7,35	7.22-7.62	618	3,9	7,8			
Creatinin	umol/L	70,6	NTP	4,7 %	F	18-59	51,1	50.2-52.0	84,1	83.0-87.0	1081	50,5	47.4-52.7	87,5	84.5-90.4	647	50	90			See table 3 and plot of enzymatic-, Vitros - and Jaffe methods on NORIP
						>=60					310										
					M	18-59	63,6	62.8-64.3	100,0	98.7-101.8	926	62,4	60.7-63.7	100,7	98.6-103.1	597	60	100			home site (1)
						>=60					317										
Iron	umol/L	21,16	NTP	5,4 %	F	18-49	9,2	8.9-9.6	33,7	33.0-34.4	2309	9,0	8.3-9.4	33,7	32.2-35.0	1076	9	34			Results <6 umol/L removed
Iron saturation		0,311		10,1 %	F	18-49	0,11	0.08-0.12	0,50	0.48-0.58	162	0,12	-	0,61	-	56	0,10	0,50			Oestrogen users and iron <6
						>=50	0,14	0.11-0.17			133						0,15				umol/L removed
					M	>=18	0,16	0.14-0.17	0,57	0.53-0.61	369	0,14	-	0,59	-	80		0,57			
Glucose	mmol/L	4,464	NTP	1,7 %	FM	>=18	3,98	3.94-4.09	5,99	5.90-6.13	918	4,18	4.14-4.36	6,29	6.12-6.52	527	4,0	6,0	4,2	6,3	Fasting (>=12 h)
					F	>=18	3,94	3.86-4.05	5,87	5.68-5.99	482	4,13	3.97-4.18	6,12	5.91-6.30	271					
					M	>=18	4,17	4.08-4.24	6,21	5.96-6.50	436	4,47	4.34-4.55	6,54	6.19-6.99	256					
HDL-cholesterol	mmol/L	1,331	NORIP	3,9 %	F	>=18	1,03	0.99-1.06	2,61	2.54-2.66	1379	1,04	0.98-1.08	2,68	2.59-2.79	644	1,0	2,7			
					M	>=18	0,83	0.79-0.86	2,13	2.05-2.16	1222	0,80	0.75-0.85	2,14	2.09-2.28	586	0,8	2,1			
Potassium	mmol/L	3,74	NTP	2,3 %	FM	>=18	3,61	3.60-3.63	4,64	4.61-4.66	2608	3,47	3.45-3.49	4,38	4.32-4.43	1172	3,6	4,6	3,5	4,4	See table 2
LDL-cholesterol	mmol/L	2,9		4,0 %	FM	18-29	1,24	1.06-1.33	4,29	3.98-4.38	275	1,21	0.58-1.36	4,00	3.68-4.30	144	1,2	4,3			
						30-49	1,39	1.28-1.68	4,71	4.39-5.11	310	1,47	1.16-1.61	4,25	3.95-4.95	159	1,4	4,7			LDLchol.=cholesterol-HDLcholesterol-triglycerides/2, where triglycerides is <4 mmol/L
						>=50	1,98	1.86-2.16	5,35	5.13-5.67	579	1,94	1.73-2.05	5,08	4.89-5.86	351	2,0	5,3			
Magnesium	mmol/L	0,797	NTP	2,6 %	FM	>=18	0,71	0.70-0.71	0,94	0.93-0.95	2123	0,71	0.71-0.72	0,93	0.93-0.94	943	0,71	0,94			
Sodium	mmol/L	137,4	NTP	0,5 %	FM	>=18	136,7	136.3-136.9	144,8	144.5-145.1	2642	136,7	136.35-137.11	143,6	143.4-143.9	1291	137	145		144	
Phosphate	mmol/L	1,03	DGKC	5,4 %	F	>=18	0,85	0.84-0.87	1,49	1.45-1.50	1365	0,76	0.72-0.78	1,41	1.37-1.45	618	0,85	1,50	0,76	1,41	
					M	18-49	0,75	0.73-0.77	1,63	1.57-1.70	670	0,71	0.69-0.73	1,53	1.45-1.59	298	0,75	1,65	0,71	1,53	
						>=50			1,33	1.31-1.39	558			1,23	1.16-1.31	271		1,35		1,23	
Protein	g/L	67,1	DGKC	2,1 %	FM	>=18	62,4	62.0-62.7	77,9	77.5-78.8	1985	64,3	63.8-64.9	79,5	79.2-80.0	877	62	78	64	79	
TIBC	umol/L	68,0	NORIP (IFCC transferrin)	4,8 %	FM	>=18	48,9	48.5-50.1	83,4	81.1-85.7	668	47,4	44.7-49.8	79,8	76.0-84.5	136	49	83	47	80	Oestrogen users removed
Triglycerides	mmol/L	1,31	DGKC	7,1 %	FM	>=18	0,47	0.44-0.48	2,60	2.35-2.86	1203	0,45	0.42-0.48	2,39	2.21-2.55	704	0,45	2,60			Fasting (>=12 hours)
Urea	mmol/L	4,8	NTP	7,9 %	F	18-49	2,66	2.47-2.71	6,41	6.09-6.71	761	2,59	2.36-2.72	6,24	5.76-6.79	276	2,6	6,4			
						>=50	3,11	2.97-3.31	7,97	7.66-8.35	585	3,05	2.68-3.38	7,40	7.23-8.70	248	3,1	7,9			
					M	18-49	3,24	3.08-3.31	8,16	7.97-8.42	649	3,21	2.97-3.50	8,08	7.50-8.87	252	3,2	8,1			
						>=50	3,64	3.46-3.78			538	3,46	3.24-3.61	8,06	7.83-9.75	230	3,5				
Uric acid	umol/L	290,2	NTP	7,2 %	F	18-49	154	148-159	350	340-365	780	160	142-168	365	333-407	280	155	350			
						>=50			394	379-414	608			421	397-456	257		400			
					M	>=18	231	225-239	475	466-481	1232	227	213-235	482	455-502	503	230	480			

Adapted from slide by Dr Ken

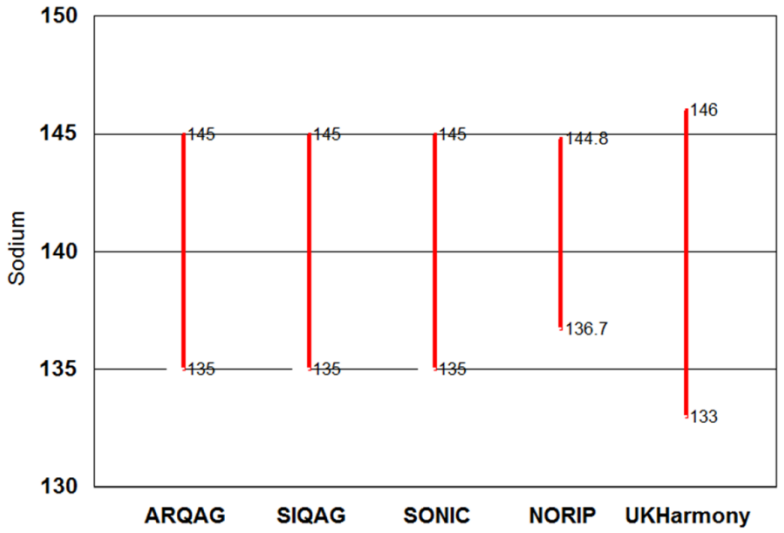
Analytical Bias & Ref Intervals: Sodium

Koerbin Bias Study



+/- 1 mmol/L

RR Consensus

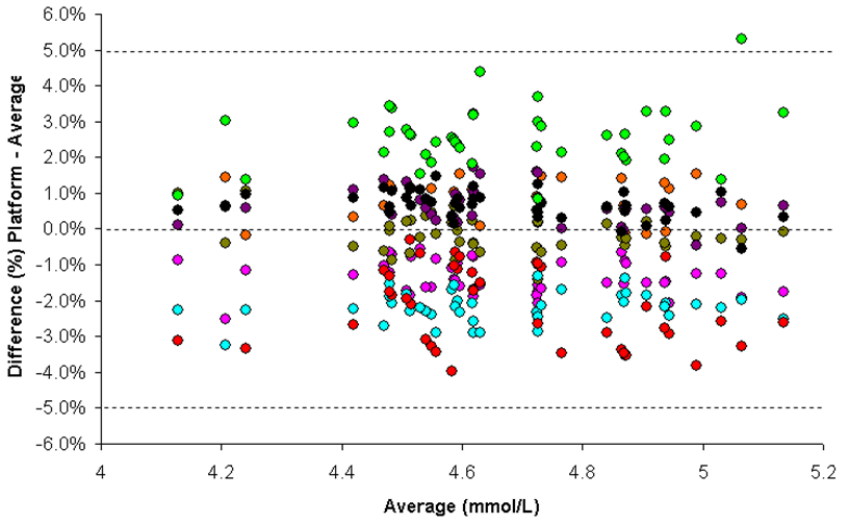


+/- 2 mmol/L

Adapted from slide by Dr Ken

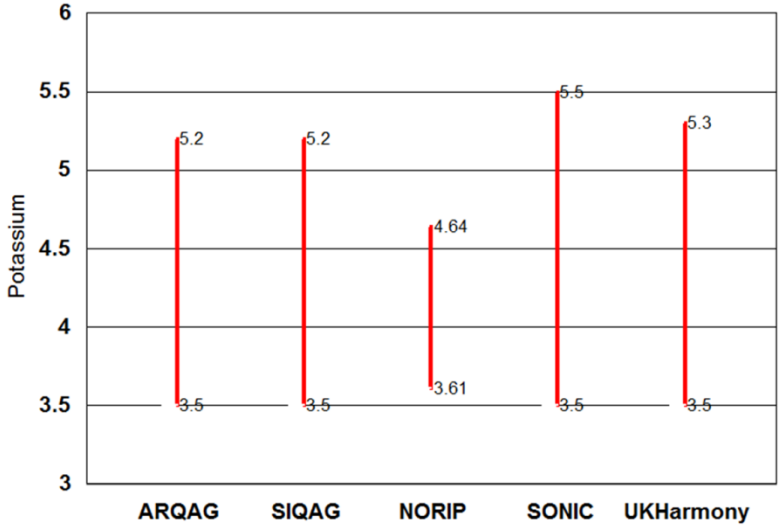
Analytical Bias & Ref Intervals: Potassium

Koerbin Bias Study



+/- 0.1 mmol/L

RR Consensus

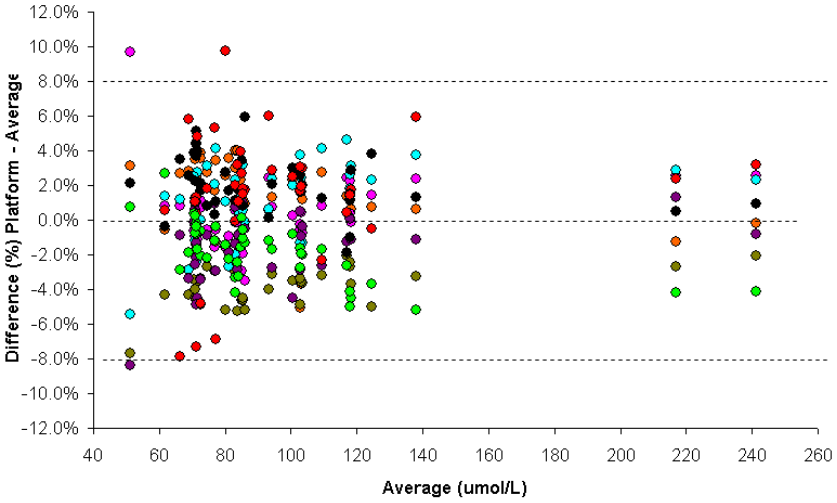


+/- 0.3 mmol/L

Adapted from slide by Dr Ken

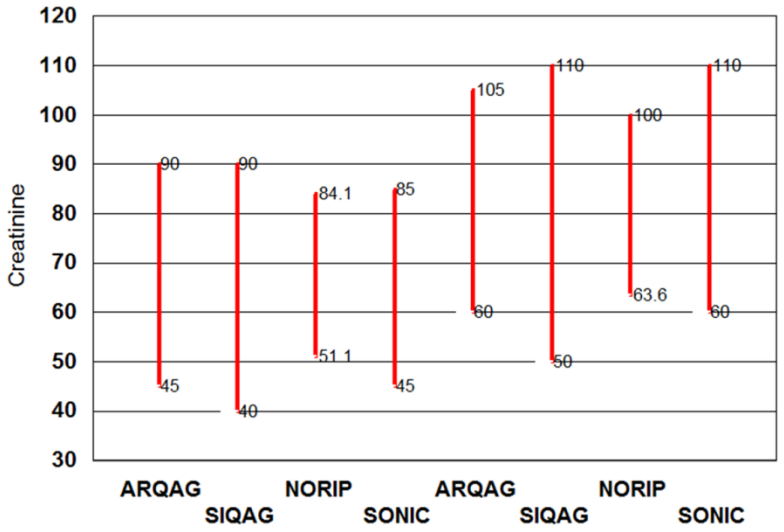
Analytical Bias & Ref Intervals: Creatinine

Koerbin Bias Study



+/- 4 µmol/L

RR Consensus

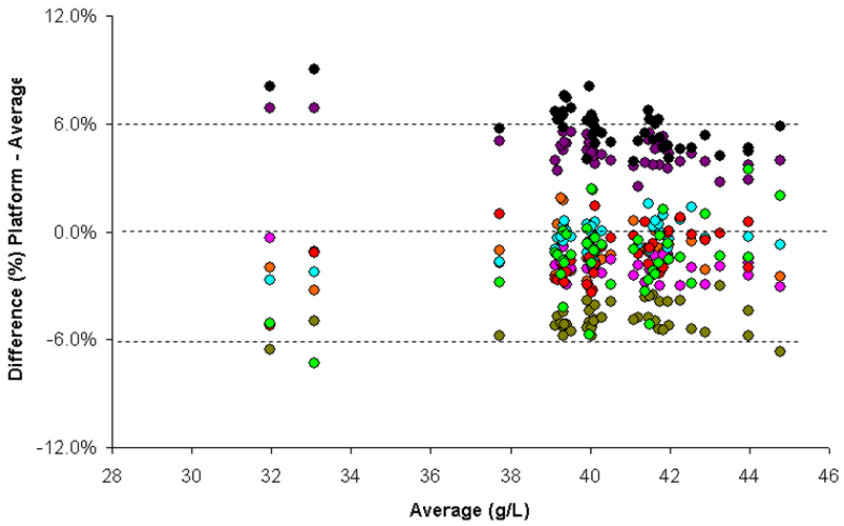


+/- 10 µmol/L

Adapted from slide by Dr Ken

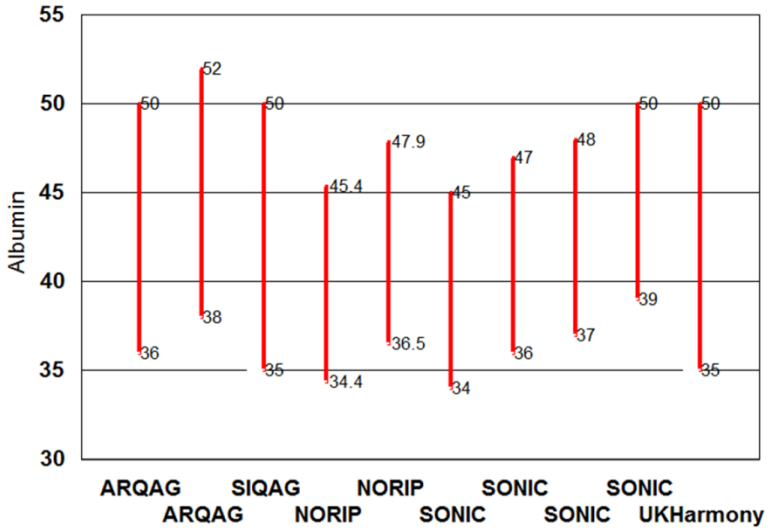
Analytical Bias & Ref Intervals: Albumin

Koerbin Bias Study



+/- 2 g/L

RR Consensus

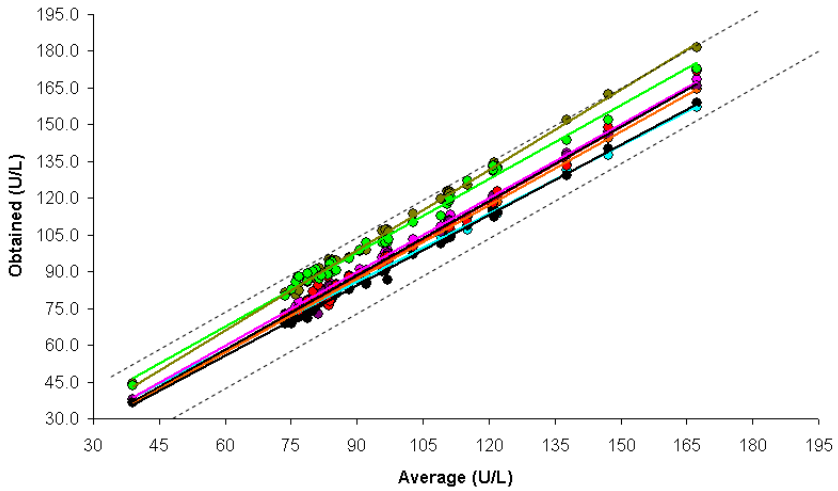


+/- 5 g/L

Adapted from slide by Dr Ken

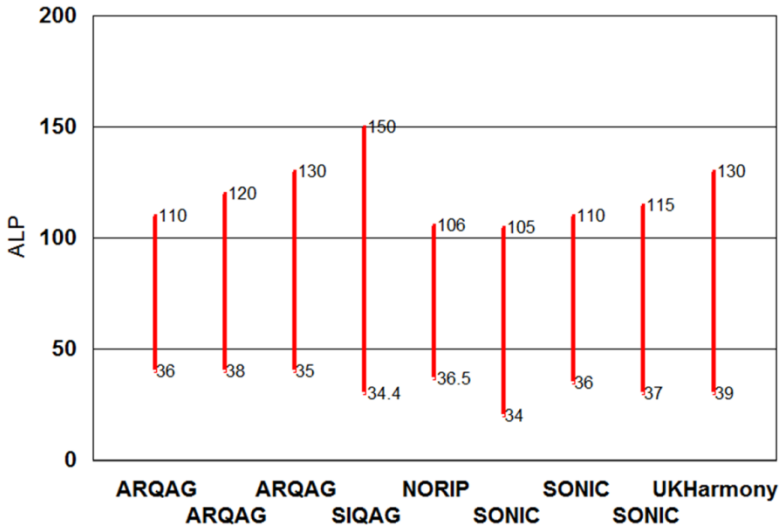
Analytical Bias & Ref Intervals: Alkaline Phosphatase

Koerbin Bias Study



+/- 5 IU/L

RR Consensus

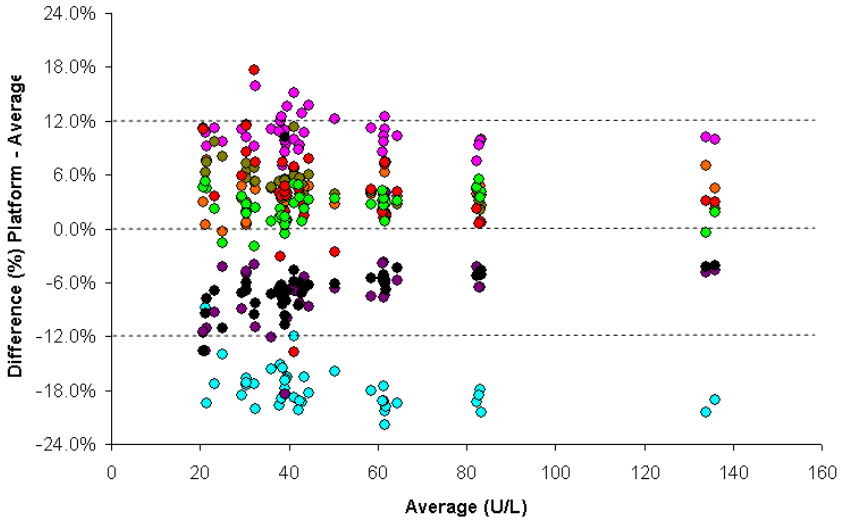


+/- 20 IU/L

Adapted from slide by Dr Ken

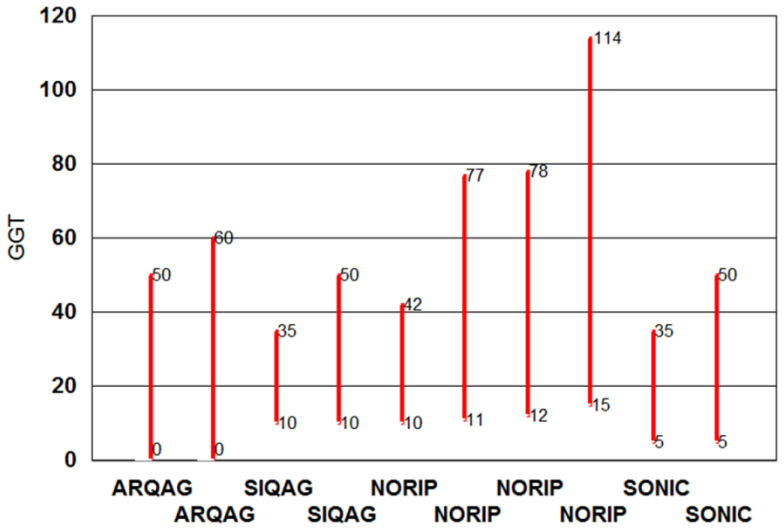
Analytical Bias & Ref Intervals: GGT

Koerbin Bias Study



+/- 5 IU/L

RR Consensus



+/- 30 IU/L

Adapted from slide by Dr Ken

Summary: Harmonised Reference Intervals

- What is necessary?
  - Appropriate reference Intervals
  - Evidence exists showing that:
    - Methods are ‘the same’
    - Populations are ‘the same’
  - The quality of common RI depends on the quality of evidence used to derive them

Do you know the source and robustness of your RI?

Is it different to your peers with the same method?

Australasian Association of Clinical Biochemists
50th Annual Scientific Conference
15-18 November 2012
Melbourne Convention & Exhibition Centre
Melbourne Victoria

towards global harmonisation

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