SONIC HEALTHCARE

1st EFLM Strategic Conference
Defining analytical performance goals 15 years after the Stockholm Conference
8th CIRME International Scientific Meeting

EFLM

Performance Criteria for: The Post-analytical Phase

A/Prof Ken Sikaris
Chemical Pathologist
Melbourne Pathology, Australia
BSc(Hons), MBBS, FRCPA, FFSc, FAACB, GAICD

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EFLM

OUTLINE

- Defining Performance Goals
  - Minimal / Desirable / Optimal
- Defining the Post-Analytical phase
  - Data, Information, Knowledge and Action
- Hierarchical Performance Criteria
  - Reference Intervals & Clinical Decision Limits
  - Significant Changes
  - Critical limits

A/Prof Ken Sikaris 25th November 2014

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10,000 Patients/Day

20,000 Patients/Day

SONIC HEALTHCARE

Sonic Healthcare

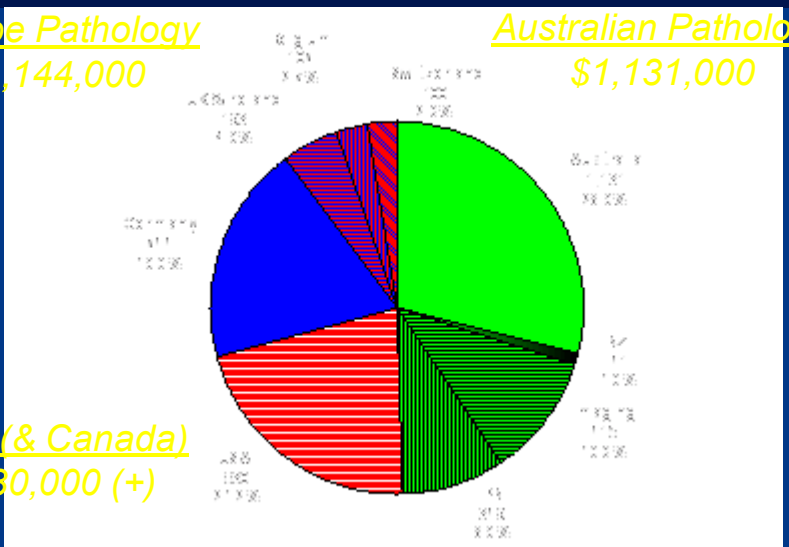
SONIC HEALTHCARE

EFLM

Sonic Healthcare

Europe Pathology
$1,144,000

Australian Pathology
$1,131,000



USA (& Canada)
$830,000 (+)

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EFLM

DEFINING PERFORMANCE *GOALS*

A/Prof Ken Sikaris 25th November 2014

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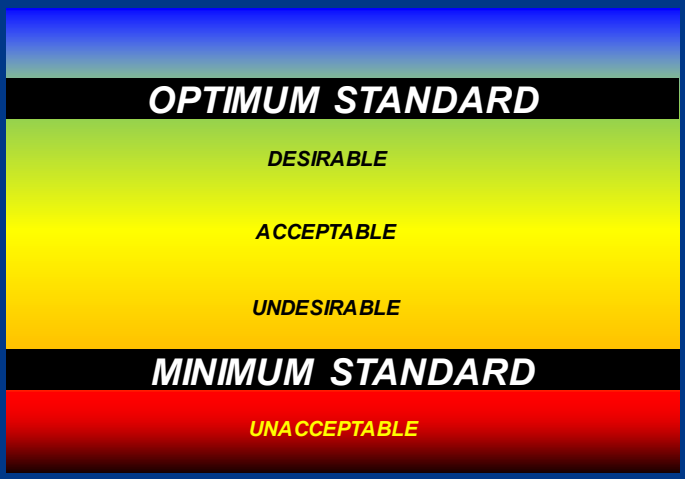
QUALITY LEVELS: General Concepts



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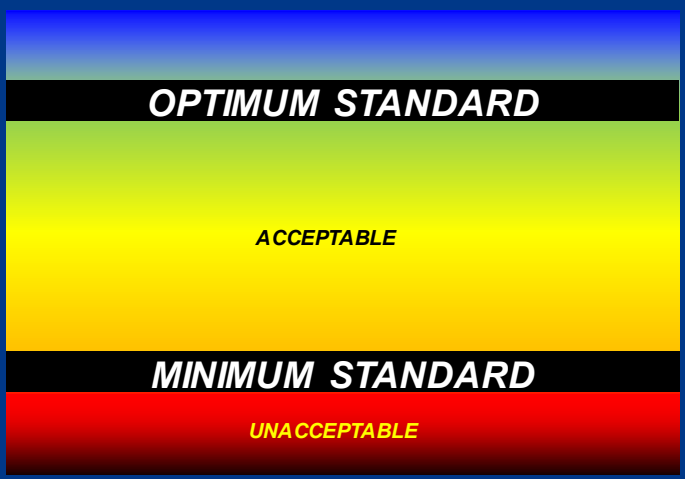
Model 3: State of the Art



Best Labs

Most Labs

Worst Labs

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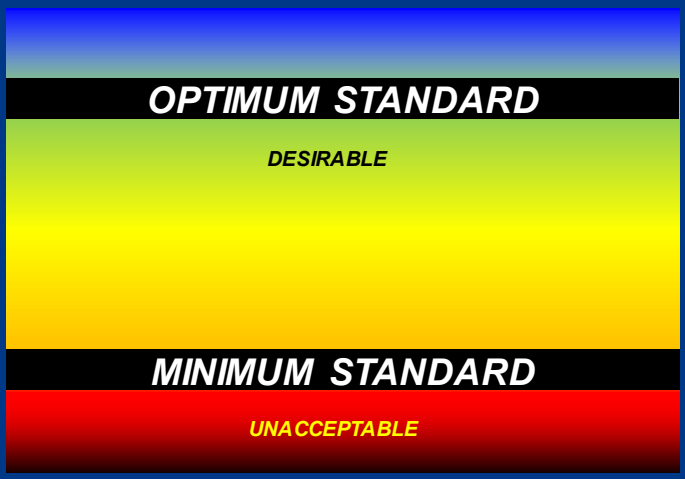
Model 2 Biological Variation



$0.25\ CV_I$

$0.5\ CV_I$

$0.75\ CV_I$

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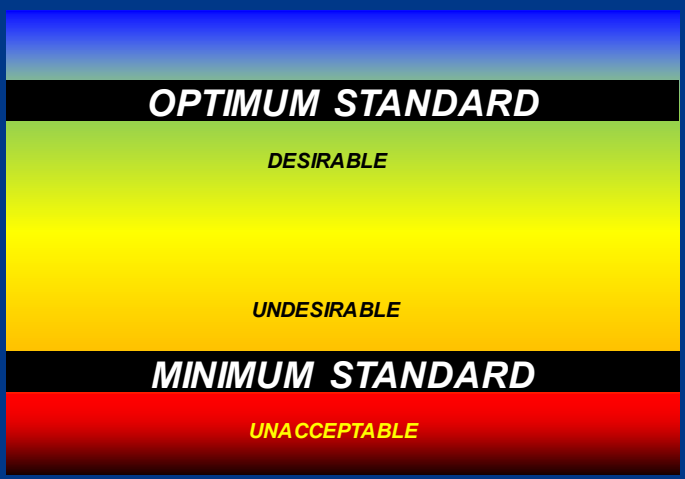
Model 1: Clinical Outcome



Health

Wellness

Unwell

Mortality

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DEFINING THE POST-ANALYTICAL PHASE

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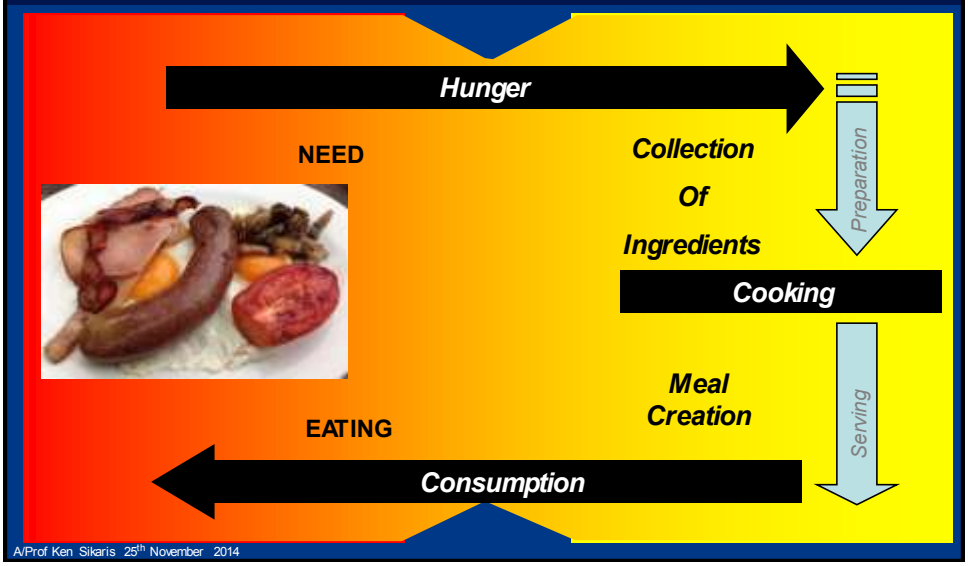
"The Brain to Brain Loop"



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EFLM

"The Brain to Brain Loop"

CLINICAL NEED

Test Selection

Sample Collection & Transport

Preanalytical

Analysis / Test Results

Report Creation

Postanalytical

CLINICAL ACTION

Report Interpretation

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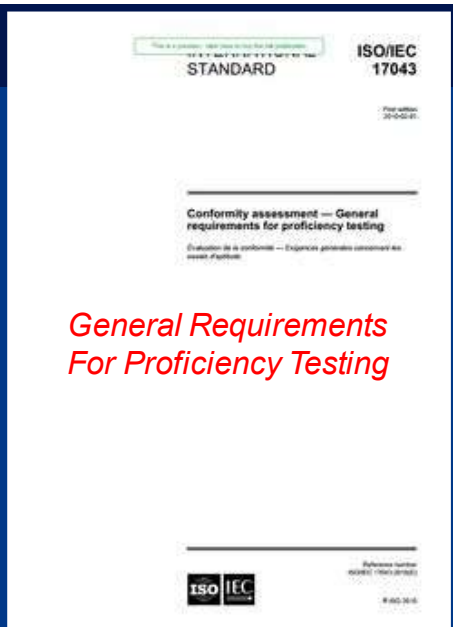
ISO 17043

Performance Goals:

Defining laboratory proficiency



General Requirements For Proficiency Testing

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ISO17043 Appendix A1

- Three basic types of laboratory examinations
  - Quantitative measurement: interval or a ratio scale.
  - Qualitative tests: ordinal or categorical scale
  - Interpretive tests concerning participant's interpretive competence.

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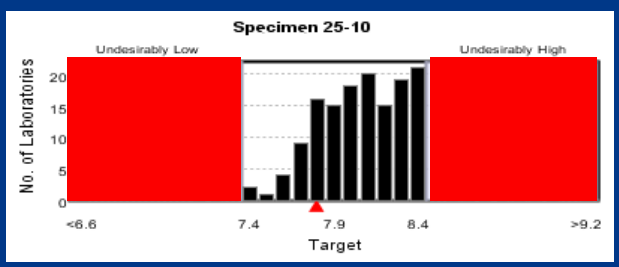
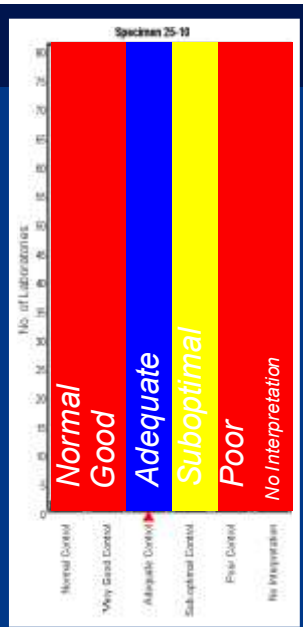
Target HbA1c = 7.9%





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Report Comments: Education/EQA

RCPAQAP

Home About News Disciplines Enrolment Careers Contact Participant Login

Chemical Pathology

- Program Organisation
- Programs
- Due Dates
- Method Classification
- Assessment of Performance
- Reports
- Program Information Circulars
- Getting Started
- Participants
- Accreditation
- History

Programs

Alcohol/Ammonia	For the analysis of alcohol and ammonia.
Basic Chemistry	Designed for very small laboratories doing a limited range of testing. Only available for laboratories outside Australia and New Zealand.
Point-of-Care Testing	Programs designed specifically for point-of-care testing instruments.
Options	Chemistry
	Troponin – TnI using the Abbott i-STAT & TnT using the Roche cobas h232.
Porphyrins	For the analysis of porphyrins, porphyrin components and patient report comments.
Options	Plasma

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CHEM - INTERPRETIVE

Case 6 **12-08-02**

Patient ID 21 year old woman

Patient Location General Practitioner

Case Details
Plasma:

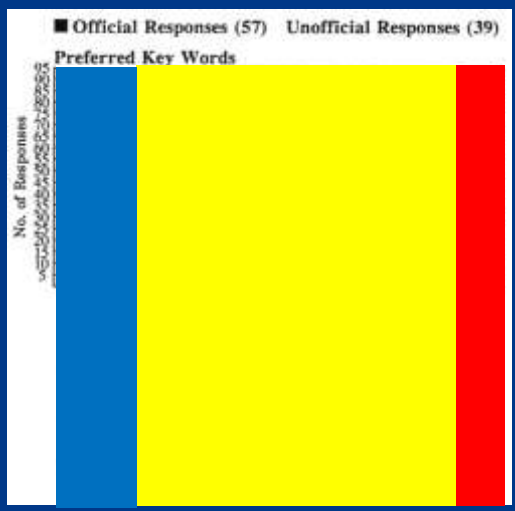
Glucose 9.2 mmol/L

Clinical Notes on Request Form
Mid-trimester screening

Additional Information
Sample taken one-hour post 75g glucose load. Not a known diabetic.

A Suggested Comment
Positive glucose challenge test, a full 2 hour 75gm glucose tolerance test is indicated.

Rationale and References
Recommendations of the Australian Diabetes in Pregnancy Society (www.adips.org) were published in the Medical Journal of Australia and are referred to by the New Zealand Society for the Study of Diabetes (www.diabetes.org.nz). A glucose level of >=8.0 at 1 hour after a 75gm load is a positive oral glucose challenge test and the patient should proceed to a full 2 hour OGTT for confirmation. It should also be noted that most women with a positive challenge do not turn out to have gestational diabetes.
References: Hoffman L, et al Med J Aust 1998;169:93-97.



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Performance Criteria:

- **Quantitative**
  - Within acceptable performance for bias
  - Within acceptable performance for imprecision
- **Categorical**
  - If they are identical, then performance is acceptable.
  - If they are not identical, then expert judgement is needed to determine if the result is fit for its intended use.

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WHO contribution

Response Evaluation

Score	Description	Criteria for assignment of score

Epidemic and Pandemic Alert and Response

World Health Organization

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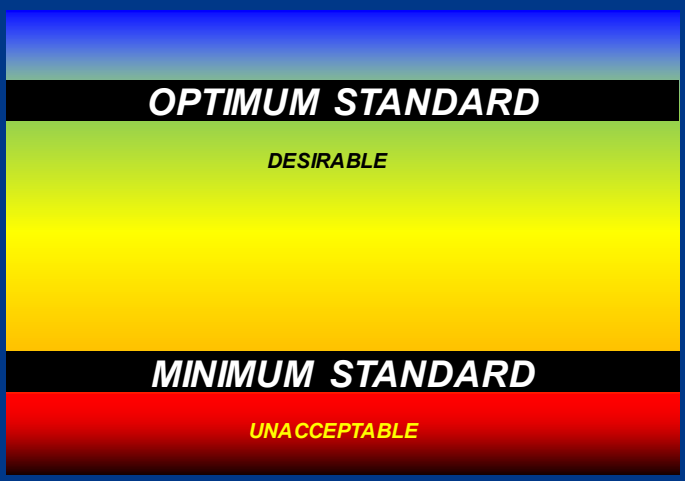
QUALITY LEVELS: Categorical



Excellent

Good

Acceptable

Poor

Bad

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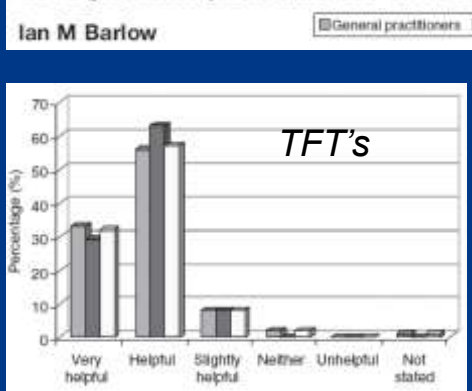
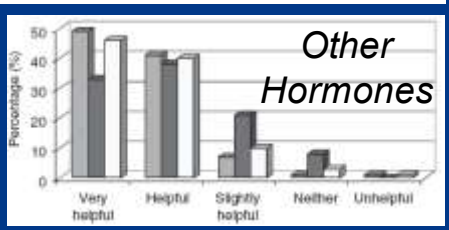
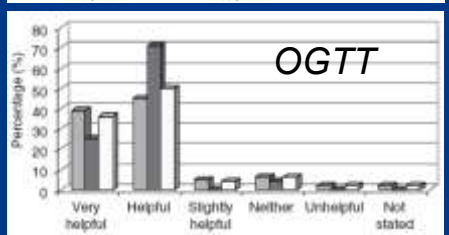
Ann Clin Biochem 2008; 45: 88–90.

Are biochemistry interpretative comments helpful? Results of a general practitioner and nurse practitioner survey

Ian M Barlow







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Ann Clin Biochem 2004; 41: 227–229

Can the addition of interpretative comments to laboratory reports influence outcome? An example involving patients taking thyroxine

ES Kilpatrick

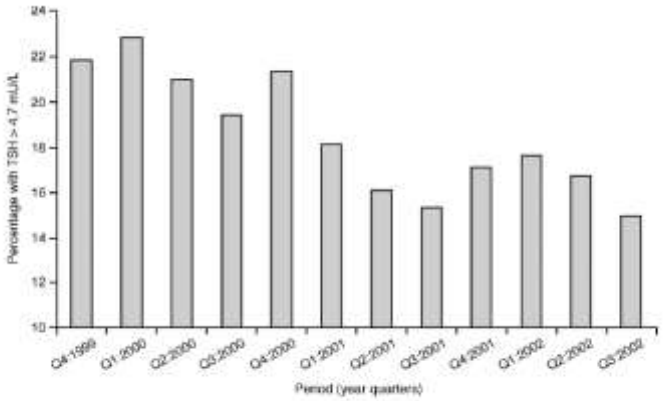

Figure 1. *Percentage of samples in patients undergoing thyroxine replacement with thyroid-stimulating hormone (TSH) concentrations of > 4.7 mU/L, following introduction of a laboratory interpretative service.*

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EFLM

Clinical Chemistry 50:3 632–637 (2004)

Quality Assessment of Interpretative Commenting in Clinical Chemistry

Ee Mun Lim,[1] Ken A. Sikaris,[2,3] Janice Gill,[3] John Calleja,[3] Peter E. Hickman,[4] John Beilby,[1,5] and Samuel D. Vasikaran[5,6]*

Table 5. Total usage of key phrases for the three categories of classification for each case, broken down by official and unofficial participants.

	Key phrases, n			
	Preferred		Less relevant	
Case	Official	Unofficial	Official	Unofficial
1	101	99	92	93
2	130	107	52	61
3	51	48	84	88
4	133	104	36	31
5	27	26	95	46
6	57	39	30	23
7	28	41	51	77
8	42	32	22	31
9	86	61	62	74
10	94	66	82	91
Total	749	623	606	615

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EFLM

Clinical Chemistry 50:3 632–637 (2004)

Quality Assessment of Interpretative Commenting in Clinical Chemistry

Ee Mun Lim,[1] Ken A. Sikaris,[2,3] Janice Gill,[3] John Calleja,[3] Peter E. Hickman,[4] John Beilby,[1,5] and Samuel D. Vasikaran[5,6]*

Conclusion: The golden rule in medicine is "do no harm". Although there is no objective evidence that interpretive comments help to improve patient outcomes, if comments are added to reports it is important that they reflect accepted practice and current guidelines.

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EFLM

Clin Chem Lab Med 2009;47(8):963–970

Quality of interpretative commenting on common clinical chemistry results in the Asia-Pacific region and Africa

Samuel D. Vasikaran[1,2,*], Leslie C. Lai[3], Sunil Sethi[4], Joseph B. Lopez[5] and Kenneth A. Sikaris[6]

Conclusions: While interpretative commenting is an important laboratory activity, the results of this study suggest that there is room for improvement in the quality of interpretative comments offered by senior laboratory professionals, even for commonly reported results relating to most prevalent and important public health conditions. and continuing professional development in this area is required for the provision of a quality interpretative service.

SONIC HEALTHCARE

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Ann Clin Biochem 2000; 37: 758–763

Provision of interpretative comments on biochemical report forms

William J Marshall[1] and Gordon S Challand[2]

SUMMARY. Providing interpretative comments on reports, particularly those for primary care physicians is an important part of our job. Few clinical biochemists (whether medical or scientific) receive significant training for this.

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Clin Biochem Rev Vol 29 Suppl (i) August 2008 I S99

Interpretative Commenting

Samuel Vasikaran

The individualised narrative interpretative comment epitomises interpretative commenting. Components of a good comment may include the following:

DATA

INFORMATION

KNOWLEDGE

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Clin Chem Lab Med 2009;47(8):963–970

Quality of interpretative commenting on common clinical chemistry results in the Asia-Pacific region and Africa

Samuel D. Vasikaran[1,2,*], Leslie C. Lai[3], Sunil Sethi[4], Joseph B. Lopez[5] and Kenneth A. Sikaris[6]

45 y/o man, PSA = 3.2 ug/L

Table 6 Examples of participant comments with designation of participant (D = Medical, S = Scientist) and mean score given by the Program Committee, together with the comment drafted by the Program Committee for case 3.

D/S	Mean score	Participants' comments
S	0	The PSA value is in normal range. It shows that patient is not having any malignancy prostate problem, but in this age group he should get it repeated every year for further safety, as this age group can have risk.
S	3.5	PSA value of 3.2 μg/L cannot rule out prostatic cancer in this age group. Family history of prostate cancer, an abnormal DRE and results of previous prostate biopsy if any help assessment of caner risk. PSA density and free-to-total PSA fraction ratio assays may further delineate risk level. Based on risk level and patient's understanding of the consequences of a cancer diagnosis, he can best determine whether urology referral for a prostate biopsy or expectant management (Truncated).
Comment drafted by the Program Committee		

PSA, prostate specific antigen; DRE, digital rectal examination.

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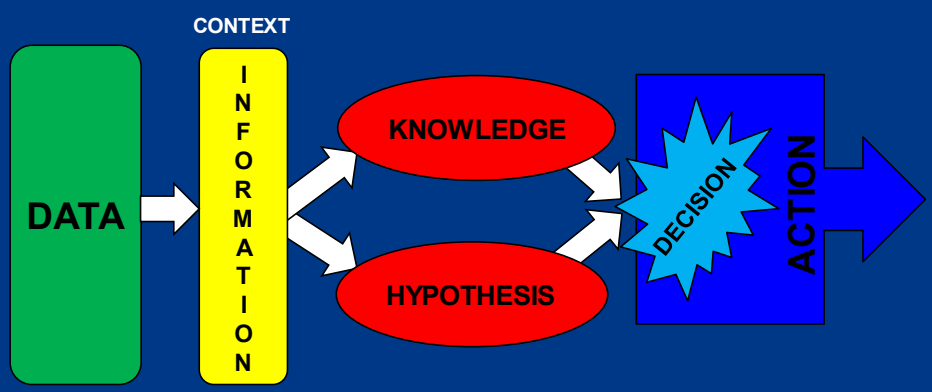
Data to Knowledge and Action:



Pathology: Data Rich, Information Poor?

J Biomed Inform. 2007 October ; 40(5): 582–602.

Conceptual Knowledge Acquisition in Biomedicine: A Methodological Review

Philip R.O. Payne, Ph.D.[1], Eneida A. Mendonça, M.D. Ph.D.[2], Stephen B. Johnson, Ph.D.[2], and Justin B. Starren, M.D. Ph.D.[3]

Figure 2. Spectrum of knowledge types
(Adapted from McCormick, "Conceptual and Procedural Knowledge", 1997)

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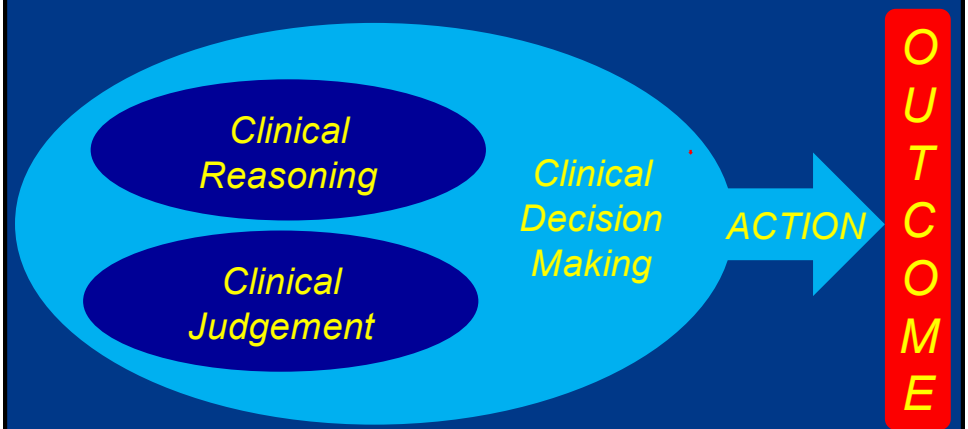
Clinical Decision Making



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HIERARCHICAL APPROACH TO POST-ANALYTICAL PERFORMANCE CRITERIA

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Why reference limits? Why flags?

Name: S ,M Dob: 16/03/79 Sex: P32
Coll: 1800,16/11/07 Doc: 0 ,D
Note: UR: 1125/6427

Date	16/11/07	
Time	1800	
Lab Id.	91911374	Units
S SODIUM	136	mmol/L
S POTASSIUM	4.5	mmol/L
S CHLORIDE	99	mmol/L
S BICARB	28	mmol/L
S UREA	3.6	mmol/L
S CREAT	57	umol/L
S eGFR	>90	
ANION GAP	14	mmol/L
T-BILI	8	umol/L
S ALP	204	U/L
S GGT	33	U/L
S ALT	78	U/L

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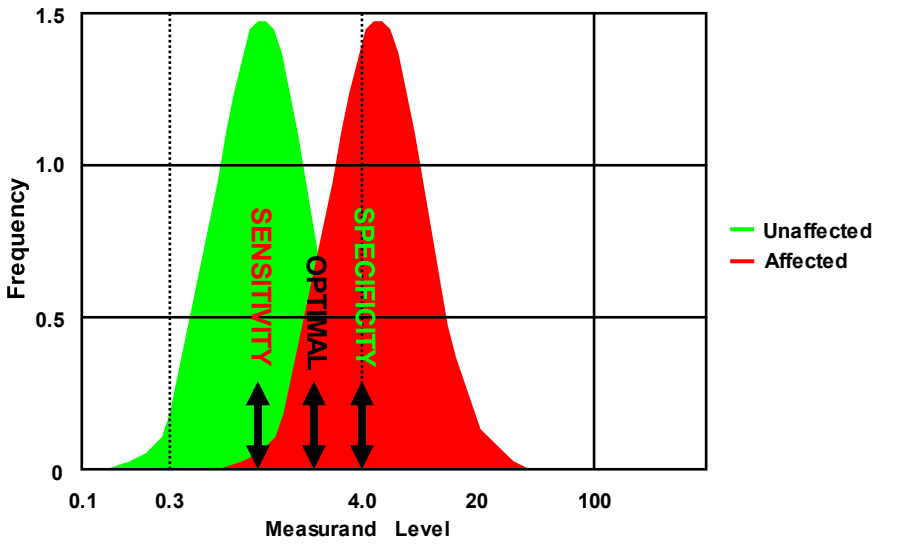

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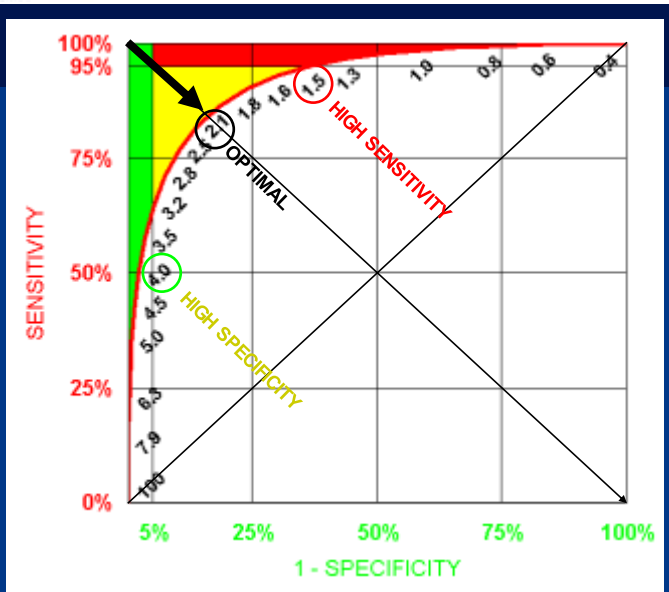

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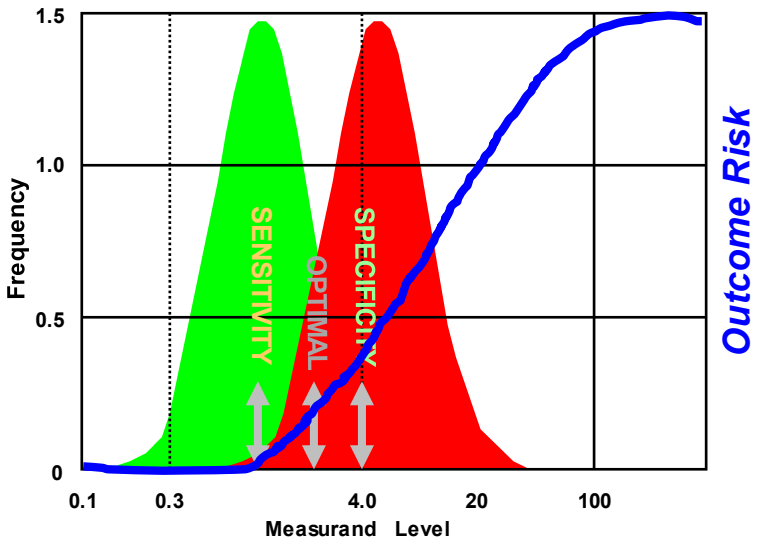

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23rd November 2014

AC Milan 1
Inter Milan 1
Crowd 75,000

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EFLM

25th April 1999

Essendon 15.18.108
Collingwood 15.10.100
Crowd 73,118

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Stockholm.

Sat 24/4/99 – Mon 26/4/99

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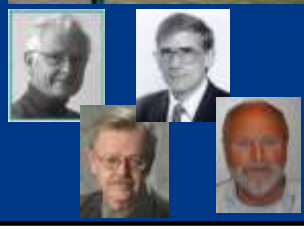
STRATEGIES TO SET GLOBAL QUALITY SPECIFICATIONS IN LABORATORY MEDICINE

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



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Clinical Biochemist Newsletter 1999;June:26-9.

Strategies To Set Global Quality Specifications
In Laboratory Medicine
IFCC Meeting 24 - 26th April 1999 Nobel Forum Karolinska Institute Stockholm, Sweden
Ken Sikaris

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Where we use performance criteria

- Method Selection
- Method Validation
- Method IQC Goals
- Monitoring across analysers / networks
- EQA Performance Goals

- Reference Intervals
- Clinical Decision Limits

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Mini-Review

Clin Biochem Rev Vol 33 November 2012 | 141

Application of the Stockholm Hierarchy to Defining the Quality of Reference Intervals and Clinical Decision Limits

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For correspondence: Dr Ken Sikaris, ken.sikaris@mps.com.au

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Stockholm Hierarchy for Analytical Quality

Table 1. The Stockholm Hierarchy for analytical quality goals. Adapted from Kenny D, et al.[10]

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 with
   a. Data derived from biological variation.
   b. Data based on clinicians' opinions.
3. Published professional recommendations
   a. National or international expert bodies.
   b. Expert local groups or individuals.
4. Performance goals set by
   a. Regulatory bodies.
   b. Organisers of external quality assurance (EQA) schemes.
5. Goals based on the current state of the art
   a. As demonstrated by data from EQA.
   b. As found in current publications.

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Stockholm Hierarchy

- Model 1: Clinical Outcome
- Model 2: Clinical Decisions
  - 2(a) Biological Variability
  - 2(b) Clinician Survey
- Model 3: Professional Recommendations
  - International / Local
- Model 4: Performance Goals
  - Regulatory / EQA
- Model 5: State of the Art

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Hierarchy for Reference Intervals & Decision Limits

Table 2. The Stockholm Hierarchy applied to reference intervals and clinical decision limits.

1. Clinical decision limit based on clinical outcome study
   e.g. HbA_{1c} cut-off based on the presence of diabetes outcome (retinopathy).[38]
2. Other methods of determining reference interval or clinical decision limit
   a. Reference intervals derived from apparently healthy populations e.g. NORIP,[39] CALIPER.[22]
   b. Clinical decision limits based on clinicians' opinions of disease e.g. thyroid-stimulating hormone (TSH) upper reference limit (2.5 mIU/L) from NACB.[31]
3. Published professional recommendations
   a. National or international expert bodies e.g. national urine protein cut-offs.[38]
   b. Expert local groups or individuals e.g. ARQAG,[41] SONIC.[42]
4. Reference limits set by
   a. Regulatory bodies e.g. prostate-specific antigen (PSA) cut-offs.[32]
   b. Formal Reference Interval Survey e.g. UK Harmony Survey.[40]
5. Reference limits based on the current state of the art
   a. Reference interval used in postanalytical external quality assurance e.g. pathology interpretation exercises.[31]
   b. Current publications on methodology e.g. textbooks or kit inserts.[34,35]

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Stockholm Hierarchy adapted

- Model 1: Clinical Outcome: Decision Limits, HbA1c
- Model 2: Clinical Decisions
  - 2(a) Biological Variability Reference Intervals
  - 2(b) Clinician Survey Expert set limits TSH 2.5 mIU/L
- Model 3: Professional Recommendations
  - International / Local Harmonised Reference Intervals
- Model 4: Performance Goals
  - Regulatory / EQA Reference Interval Survey
- Model 5: State of the Art Published Ref Int.

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Proposed Hierarchy

- Model 1: Clinical Outcome
  - Outcome Studies
  - Simulation Studies
  - Clinician Survey / Expert Opinion
- Model 2: Biological Variation
- Model 3: State of the Art

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Model 1: Clinical Outcome

a. [redacted] – investigating the impact of analytical performance of the test on clinical outcomes

b. [redacted] – investigating the impact of analytical performance of the test on the probability of clinical outcomes

c. [redacted] – investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)

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Proc ACB National Meeting 2007

Reference ranges in the real world

A Ellis
UK NEQAS for Peptide Hormones and Related Substances, Department of Clinical Biochemistry, Royal Infirmary, Edinburgh EH16 4SA

a recent survey of participants in the UK NEQAS for FSH and LH revealed that only 32% of laboratories had performed full in-house studies. The majority (52%) used data provided by the manufacturer of their current method whilst 16% relied on data from the scientific literature. In addition, some laboratories referred to historical data derived experimentally for assays no longer in use.

UK: FSH & LH

32% - In house
52% - Manufacturer
16% - Literature

My accreditation experience:

1/3rd In-House Study *(staff)*
1/3rd Historical *(can't remember)*
1/3rd Manufacturer *(+/- validation)*

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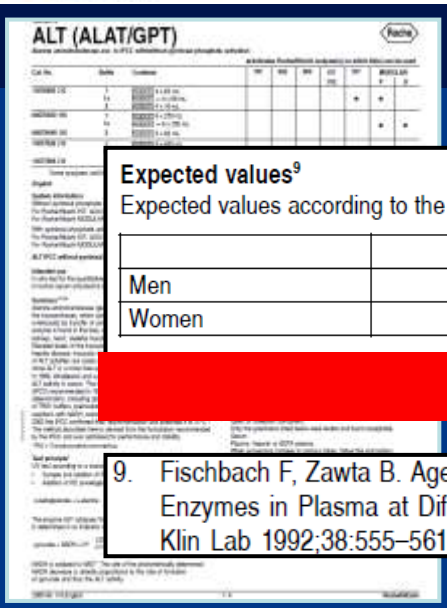
Kit Inserts


ALT (ALAT/GPT)

Expected values[9]

Expected values according to the IFCC method (measured at 37°C):

	U/L	µkat/L
Men	up to 41	up to 0.68
Women	up to 31	up to 0.52

9. Fischbach F, Zawta B. Age-dependent Reference Limits of Several Enzymes in Plasma at Different Measuring Temperatures. Klin Lab 1992;38:555–561.

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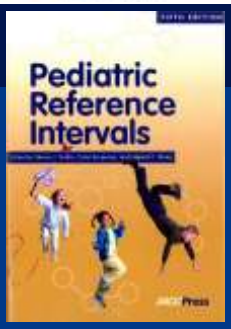
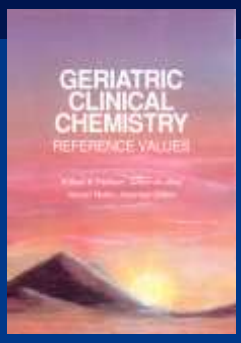
Textbooks





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CLSI C28-A3

Defining, Establishing, and Verifying Reference Intervals in the Clinical

10 Transference

As more new tests and methods are introduced in more laboratories, it is unrealistic to expect each laboratory, large and small, to develop its own reference intervals. Consequently, clinical laboratories may rely more and more on other laboratories or diagnostic test manufacturers to generate and provide appropriate and adequate reference value data that can be transferred.

CLINICAL AND LABORATORY STANDARDS INSTITUTE

ifcc

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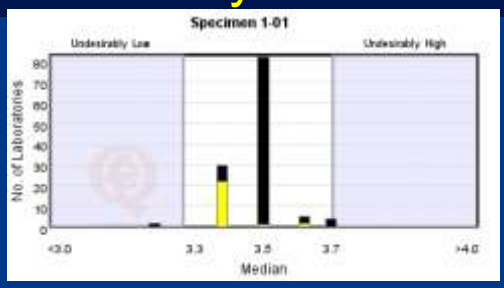
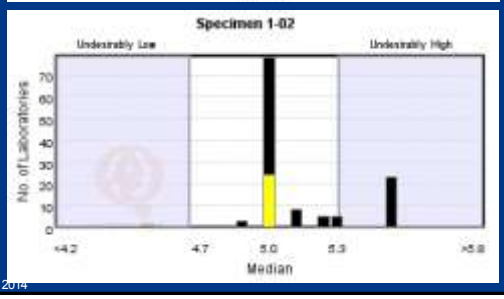
RCPAQAP Survey 2013: Potassium

Vitros Labs



Low



High

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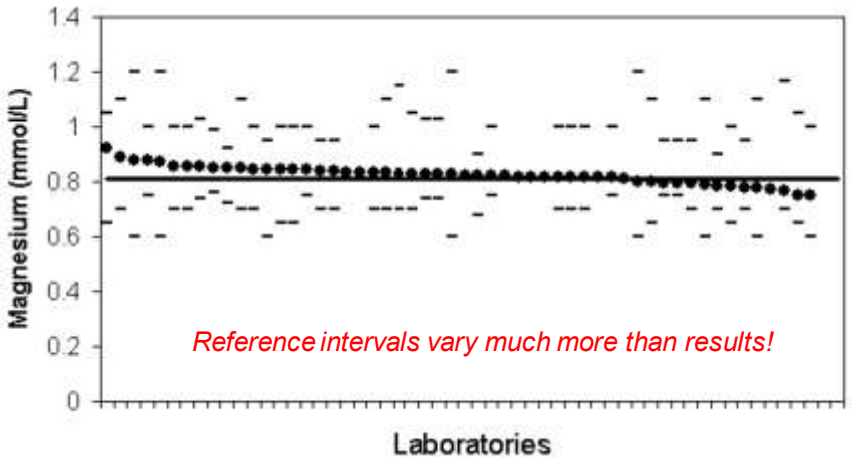
Clin Biochem Rev Vol 25 May 2004 | 99

The Case for Common Reference Intervals

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



IMEP-17

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BEYOND ANALYTICAL QUALITY: THE IMPORTANCE OF POSTANALYTICAL QUALITY IN ASSURING CLINICAL VALUE

George S. Cembrowski, MD, PhD

Tables 1 & 2 Common tests with Highest and Lowest Variation in the Male Upper Reference Limit

Tests	Highest CV%	Test	Lowest CV%
Cholesterol (total)	276.6	Cortisol (AM values)	11.2
Prolactin	220.6	Fibrinogen	10.2
Folate	176.8	Valproate	9.3
Lipase	95.7	Iron	9.2
Bilirubin (conjugated)	86.3	Platelet count	8.7
Thyroid Stimulating Hormone	73.7	HbA1c	8.6
Lactate Dehydrogenase	46.2	Theophylline	7.2
LH (follicular phase)	43.8	Phenobarbitone	7.2
FSH (follicular phase)	37.4	PSA	6.3
Amylase	35.3	Bicarbonate (total CO_2)	6.2
WBC count	33.6	Phosphate	5.1
Creatine Kinase (total)	28.0	Albumin	5.0
Magnesium	27.1	Hemoglobin	4.4
Alanine aminotransferase	23.9	Hematocrit	3.8
Ammonia	23.0	Protein (total)	3.2
Ferritin	22.9	Potassium	3.1
Gamma glutamyl transferase	22.6	Calcium	2.4
Aspartate Transaminase	18.8	Chloride	1.7
Lithium	18.5	Osmolality	1.6
Alkaline Phosphatase	17.4	Sodium	0.9

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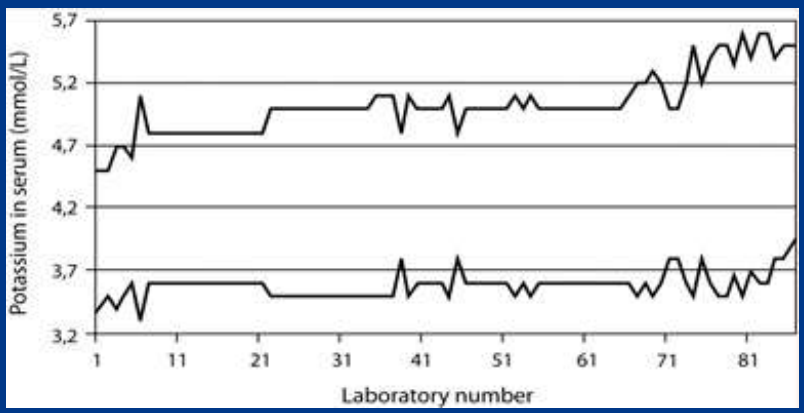
Germany



5.6

4.5

3.9

3.3

Sonntag O, J Lab Med 2003;28:302-10

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Annals of Clinical Biochemistry 2011; 48: 195–197

Pathology Harmony; a pragmatic and scientific approach to unfounded variation in the clinical laboratory

Jonathan Berg and Vanessa Lane

Potassium ranges for 45 laboratories in central England

Table 1 Examples of agreed Pathology Harmony clinical biochemistry reference intervals for adults

Test name	Units	Range low	Range high	Comments
Potassium	mmol/L	3.5	5.3	

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Model 2: Biological Variability

a. [redacted] – investigating the impact of analytical performance of the test on clinical outcomes

b. [redacted] – investigating the impact of analytical performance of the test on the probability of clinical outcomes

c. [redacted] – investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)

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Clin Chem Lab Med 2004;42(7):758–764

Inherent biological variation and reference values

Callum G. Fraser*

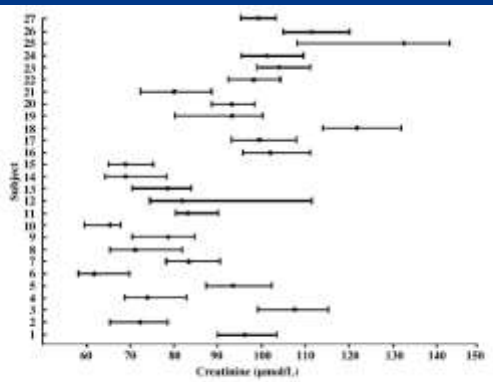

Figure 1 Means and extreme values for serum creatinine in 27 elderly people. From: Fraser CG. Biological variation in the elderly: implications for reference values. In: Faulkner WR, Meites S, editors. Geriatric clinical chemistry reference values. AACC Press: Washington, DC, 1994:p44.

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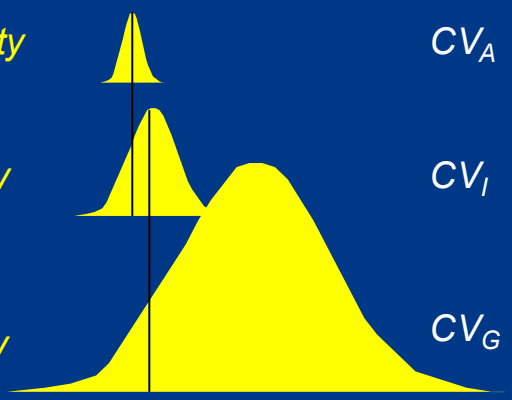
Biological Variability & Reference Intervals

Measurement Uncertainty — CV_A

Intra-individual Variability — CV_I

Inter-individual Variability — CV_G



Reference Interval includes $[(CV_A)^2 + (CV_I)^2 + (CV_G)^2]^{0.5}$

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Clin Chem Lab Med 2004;42(7):783–791

Proposal for guidelines to establish common biological reference intervals in large geographical areas for biochemical quantities measured frequently in serum and plasma

Pål Rustad[1,*], Peter Felding[2] and Ari Lahti[3]

To introduce biological reference intervals, laboratories should verify that their measurement systems fulfill criteria for metrological quality such as metrological variation (s_M) and method bias (B). The following quality goals, based on the standard deviation of biological variation (s_B), have been suggested (20):

Goal for metrological variation: $s_M < s_B/2$

Goals for method bias:

Optimum: $|B| < 0.125 \cdot s_B$
Desirable: $|B| < 0.250 \cdot s_B$
Minimum: $|B| < 0.375 \cdot s_B$

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Clin Chem Lab Med 2004;42(7):858–862

Analytical quality specifications for common reference intervals

Carmen Ricós[1,*], Maria Vicenta Doménech[2] and Carmen Perich[3]

From Gowans EM, Hyltoft Petersen P, Blaaberg O, Horder M, "Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area." Scand J Clin Lab Invest. 1988 Dec;48(8):757-64.

Maximum imprecision (with no bias) of CV_A

$$< 0.58\ (CV_I^2 + CV_G^2)^{1/2}$$

Maximum bias (with no imprecision) of SE_A

$$< 0.25\ (CV_I^2 + CV_G^2)^{1/2},$$

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Reference Intervals & Biological Variability

- Ideally personalised limits
  - Reference intervals don't work if CV_I is very small
- Index of Individuality (II) = CV_I/CV_G
  - Reference intervals most useful when II<0.6
  - Can be improved by limiting CV_G
  - Partition reference intervals (physiology)
    - Gender, Children, Adults, Pregnancy, Elderly

Harris EK. Clin Chem 1974;20:1535-42.
Petersen PH, Sandberg S, Fraser CG, Goldschmidt H. Clin Chem Lab Med 2001;39:160-5.
Fraser CG. Clin Chem Lab Med 2004;42:758-64.

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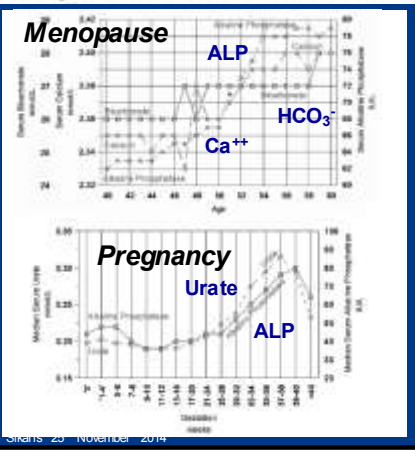
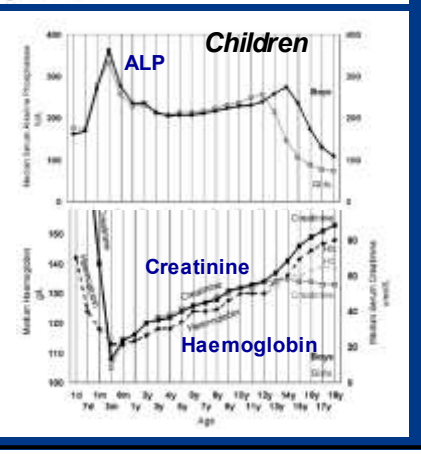
Clin Biochem Rev 35 (1) 2014 3

Physiology and its Importance for Reference Intervals

Kenneth A Sikaris
Sonic Healthcare and Department of Pathology, University of Melbourne, Vic. 3010, Australia.
For correspondence: Dr Ken Sikaris, Ken.Sikaris@mps.com.au





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Model 1: Clinical Outcome

a. [redacted] – investigating the impact of analytical performance of the test on clinical outcomes

b. [redacted] – investigating the impact of analytical performance of the test on the probability of clinical outcomes

c. [redacted] – investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)

[redacted]

[redacted]

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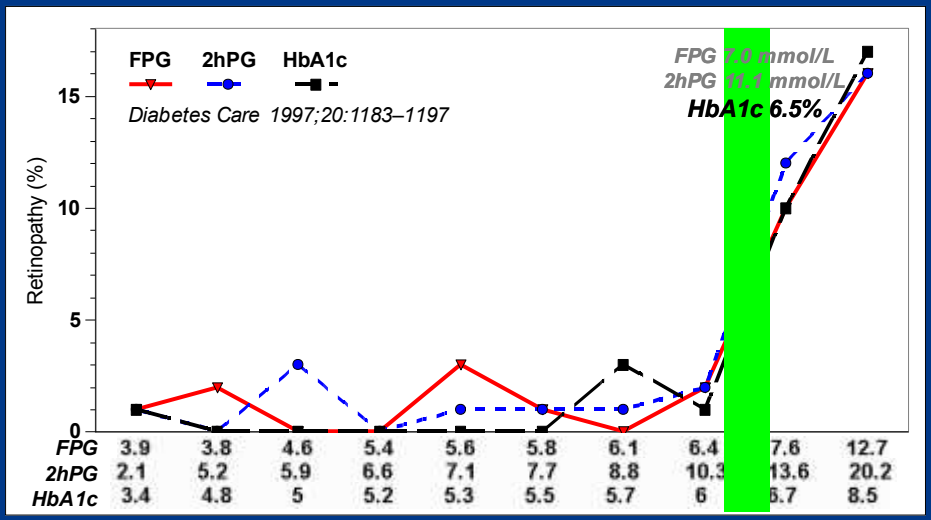
Retinopathy – Pima Indians



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Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study

Andrew J Vickers, associate attending research methodologist,[1] Angel M Cronin, research biostatistician,[1] Thomas Björk, senior consultant,[2] Jonas Manjer, associate professor,[2] Peter M Nilsson, professor,[2] Anders Dahlin, data manager,[2] Anders Bjartell, professor,[2] Peter T Scardino, department chair,[3] David Ulmert, research fellow/resident,[4,5] Hans Lilja, attending research clinical chemist/professor (adjunct)[4-7]

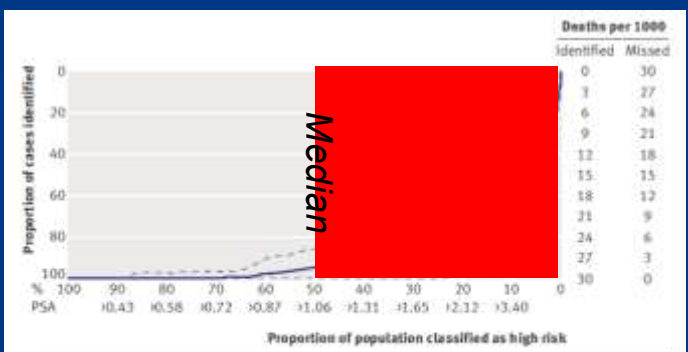

Fig 4 | Lorenz curve for death from prostate cancer: x axis shows percentage of population with prostate specific antigen (PSA) above indicated concentrations, hence percentages run from 100 down to 0; y axis shows number of events that would be included (or missed) if we consider only men with prostate specific antigen above any given concentration

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Model 1c: Clinician Survey / Expert Opinion

a. [redacted] – investigating the impact of analytical performance of the test on clinical outcomes

b. [redacted] – investigating the impact of analytical performance of the test on the probability of clinical outcomes

c. [redacted] – investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)

[redacted]

[redacted]

Guideline Addendum

2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006

Derek P. Chew, MPH, FRACP, FACC, FCSANZ[a], Constantine N. Aroney, MD, FRACP[b], Philip E. Aylward, FRACP, FCANZ, FRCP, FACC[a], Anne-Maree Kelly, MClinEd, FACEM, FCCP[c], Harvey D. White, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZ[c], Philip A. Tideman, FRACP[d], Jill Waddell, MPH[f], Leva Azadi, MPH[f], Alison J. Wilson, MBA[f,*] and Leah-Anne M. Ruta, PhD[f]

Table 1. *Summary of Recommendations.*

Recommendation	Grade
Investigations: serum troponin measurement	
Where available, high sensitivity troponin assays should be used in preference to conventional assays.	N/A
When using high sensitivity troponin assay, a test should be interpreted as positive if [redacted] OR there is a change of >50% above an initial baseline level.	Consensus
At 3 hours after presentation (with at least one assay performed >6 hours from symptom onset), a test using a high sensitivity troponin assay should be interpreted as negative if the level is <99th percentile AND change from baseline is <50%.	C

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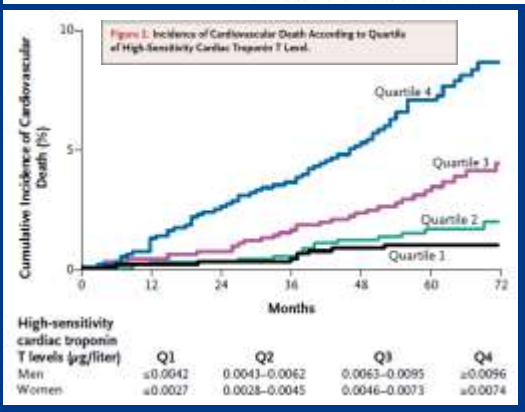
N Engl J Med 2009;361.

A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

for the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators



Men: >9 ng/L, Women: >7 ng/L

Men: 6-9 ng/L, Women: 5-7 ng/L

Men: 4-5 ng/L, Women: 3-4 ng/L

Men: <4 ng/L, Women: <3 ng/L

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pathologyharmony.co.uk

working to harmonise standards in UK pathology

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

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AACB Harmonised Reference Interval Consensus

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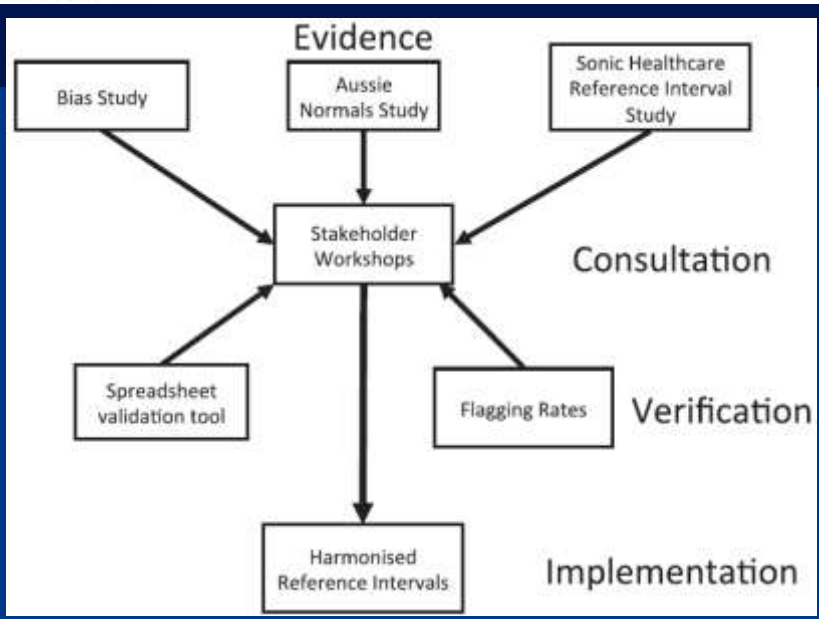

Australian reference intervals in healthy adults (ARIA) study

	ARIA (ADULT)		
	Combined	Male	Female
Na	135 - 144		
K	3.6 - 4.9		
Cl	100 - 109		
CO2	20 - 29		
Urea		4.0 - 9.1	3.2 - 8.4
Urea <60 Y		3.9 - 8.8	3.0 - 7.3
Urea >60Y		4.2 - 9.3	3.6 - 8.9
Creatinine		65 - 107	56 - 88
ALT		12 - 59	8 - 43
AST		14 - 47	13 - 37
ALP	39 - 111		
GGT (New)*		12 - 71	8 - 35
CK		46 - 295	37 - 250
LD (L-P)	124 - 232		
Tot. Protein	62 - 78		
Albumin (BCG)	39 - 50		
Ca	2.19 - 2.56		
PO4	0.82 - 1.40		
Mg	0.77 - 1.04		
Urate		200 - 486	129 - 371

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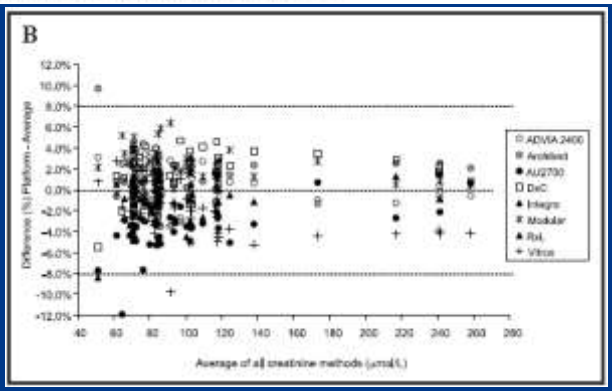
Clin Biochem Rev 35 (4) 2014 213

Harmonising Adult and Paediatric Reference Intervals in Australia and New Zealand: An Evidence-Based Approach for Establishing a First Panel of Chemistry Analytes

***Jillian R Tate,[1] Ken A Sikaris,[2] Graham RD Jones,[3] Tina Yen,[4] Gus Koerbin,[5] Julie Ryan,[6] Maxine Reed,[7] Janice Gill,[8] George Koumantakis,[9] Peter Hickman,[10] Peter Graham,[11] on behalf of the AACB Committee for Common Reference Intervals**



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Australasian Harmonised Reference Intervals

Analyte	Male	Female
Sodium	135 – 145 mmol/L	
Potassium (serum)	3.5 – 5.2 mmol/L	
Chloride	95 – 110 mmol/L	
Bicarbonate	22 – 32 mmol/L	
Creatinine	60 – 110 umol/L	45 – 90 umol/L
Calcium	2.10 – 2.60 mmol/L	
Calcium (albumin adjusted)	2.10 – 2.60 mmol/L	
Phosphate	0.75 – 1.50 mmol/L	
Magnesium	0.7 – 1.1 mmol/L	
LD [L to P] (IFCC)	120 – 250 U/L	
ALP	30 – 110 U/L	
AST*	<40 U/L	<35 U/L
ALT*	<40 U/L	<30 U/L
Total Protein	60 – 80 g/L	

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Primary role of reference intervals

- Initially use reference interval
  - We don't know what this patients result should be
  - Compare this first result to similar people
- Subsequently use previous result as baseline
  - What is a significant change?

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Clin Chem Lab Med 2004;42(7):758–764

Inherent biological variation and reference values

Callum G. Fraser*

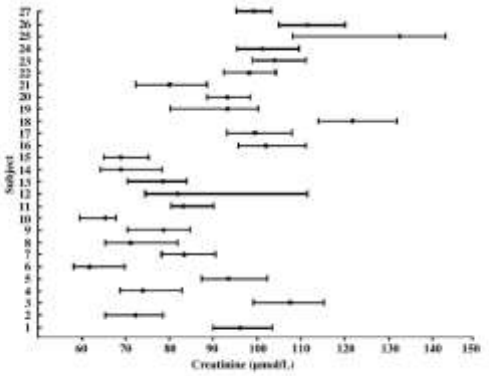

Figure 1 Means and extreme values for serum creatinine in 27 elderly people. From: Fraser CG. Biological variation in the elderly: implications for reference values. In: Faulkner WR, Meites S, editors. Geriatric clinical chemistry reference values. AACC Press: Washington, DC, 1994:p44.

Significant Change: Biological

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Post-analytical: Significant Change

- Clinical Outcome
- Biological Variation
- State of the Art

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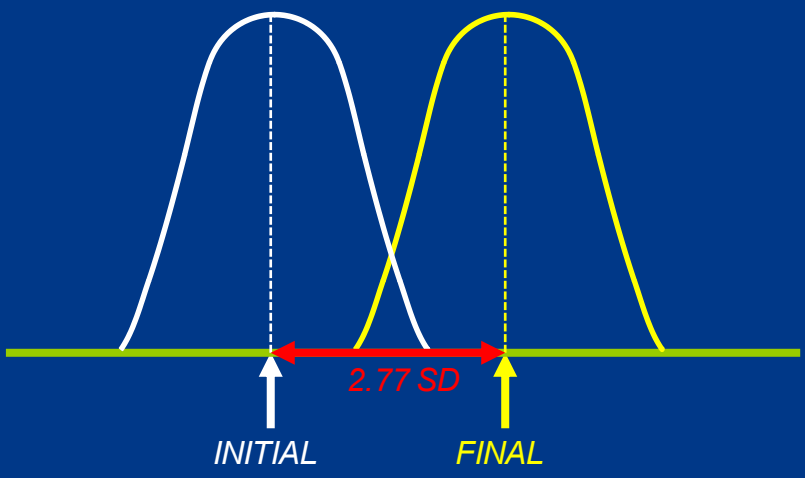
Significant Change



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Significant Change: Biological Variability

Analyte	CV_A	CV_I	RCV
Albumin	0.8%	3.1%	8.6%
ALP	1.4%	6.4%	18.1%
Bilirubin	1.0%	25.6%	70.9%
ALT	0.9%	24.3%	67.3%
AST	1.1%	11.9%	33.2%

Significant Change: Biological

Guideline Addendum

Significant Change: Clinician Survey

2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006

Derek P. Chew, MPH, FRACP, FACC, FCSANZ[a], Constantine N. Aroney, MD, FRACP[b], Philip E. Aylward, FRACP, FCANZ, FRCP, FACC[a], Anne-Maree Kelly, MClinEd, FACEM, FCCP[c], Harvey D. White, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZ[c], Philip A. Tideman, FRACP[d], Jill Waddell, MPH[f], Leva Azadi, MPH[f], Alison J. Wilson, MBA[f,*] and Leah-Anne M. Ruta, PhD[f]

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At 3 hours after presentation (with at least one assay performed >6 hours from symptom onset), a test using a high sensitivity troponin assay should be interpreted as negative if the level is <99th percentile AND change from baseline is <50%.	C

A/P

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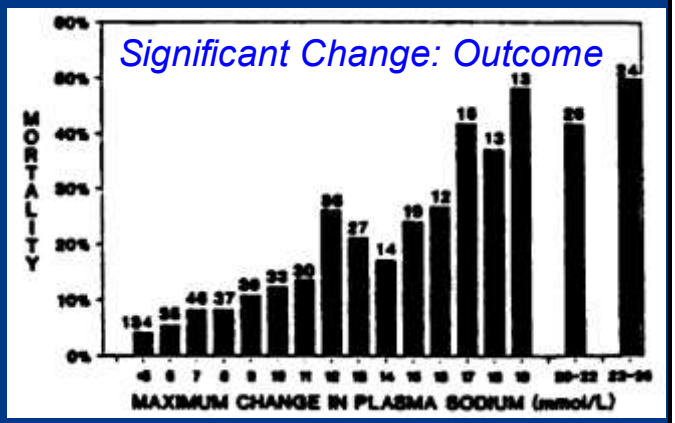
Change in Plasma Sodium Associated with Mortality.

Guerin MD, Martin AL, Sikaris KA, Clin Chem 1992;38:317

Significant Change: Outcome



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Watchful Waiting or Watchful Progression?

Prostate Specific Antigen Doubling Times and Clinical Behavior in Patients with Early Untreated Prostate Carcinoma *Cancer* 1998;82:342–8.

Duncan B. McLaren, F.R.C.R.
Michael McKenzie, F.R.C.P.C.
Graeme Duncan, F.R.C.P.C.
Tom Pickles, F.R.C.P.C.

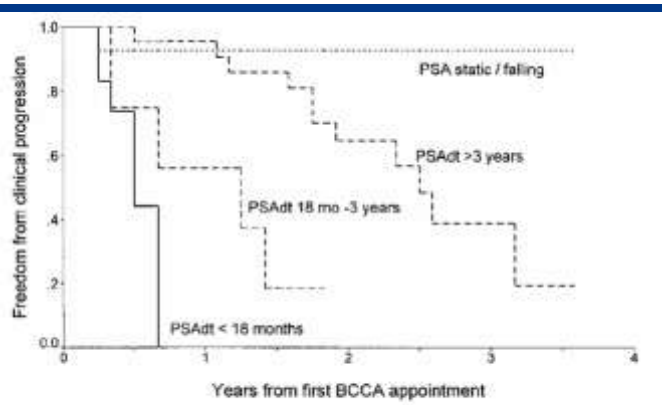

FIGURE 2. Graph of time to clinical progression based on prostate specific antigen doubling time (PSAdt). BCCA: British Columbia Cancer

Significant Change: Outcome

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Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art

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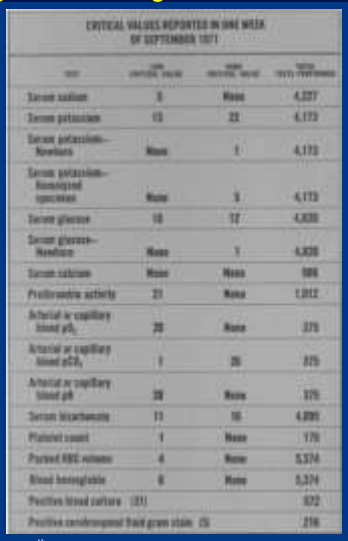
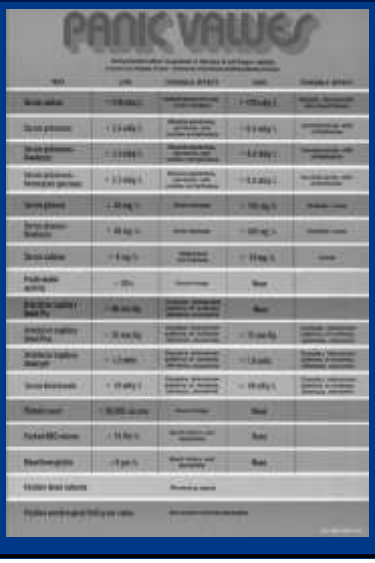
When to panic over an abnormal result.

George D Lundberg, Med Lab Obs 1972;





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Survey of laboratory 'critical limits'.

Tillman & Barth Ann Clin Biochem 2003;40:181-184.

- No consensus in UK
  - All labs have common tests
    - Na, K, Glu, (Ca)
  - Wide variation in common tests
    - Na 147 – 170, K 5.5 – 7.0
  - Similar to previous US reports.
  - Universal standards could be agreed.

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Laboratory Critical Values.

Arch Pathol Lab Med 2002;126:663-669.

SOURCE OF CRITICAL LIST

- 20% Literature only
- 36% Literature & Laboratory meeting
- 17% Literature & Hospital committee
- 73% Literature, Laboratory & Medical

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Arch Pathol Lab Med. 2007;131:1769–1775

Critical Values Comparison

A College of American Pathologists Q-Probes Survey of 163 Clinical Laboratories

Elizabeth A. Wagar, MD, FCAP; Richard C. Friedberg, MD, PhD, FCAP; Rhona Souers, MS; Ana K. Stankovic, MD, PhD, FCAP

Table 4. Adult and Pediatric Median Critical Values

Analyte	Low Critical Value Percentiles: No. of Institutions	5th	50th (Median)	95th	High Critical Value Percentiles: No. of Institutions	5th	50th (Median)	95th
Adult Critical Values Summary								
Calcium, mg/dL	160	6.0	6.1	7.1	161	12.0	13.0	14.0
Magnesium, mEq/L	124	0.7	0.8	1.1	125	2.5	4.1	5.8
Hemoglobin, male patients, g/dL	157	5.0	7.0	8.0	115	18.0	20.0	23.0
Hemoglobin, female patients, g/dL	155	5.0	7.0	8.0	113	18.0	20.0	23.0
Platelet count, $\times 10^9$/μL	162	20	31	70	131	700	999	1000
Activated partial prothrombin time, s	17	5	18	22	154	42	90	150
Pediatric Critical Values Summary								
Potassium, mEq/L	144	2.5	2.9	3.1	143	5.9	6.0	6.3
Calcium, mg/dL	142	6.0	6.1	7.1	143	12.0	13.0	14.0
Magnesium, mEq/L	109	0.7	0.8	1.1	109	2.5	4.0	6.1
Hemoglobin, male patients, g/dL	143	5.0	7.0	8.1	98	18.0	20.0	25.0
Hemoglobin, female patients, g/dL	143	5.0	7.0	8.1	99	18.0	20.0	25.0
Platelet count, $\times 10^9$/μL	146	20	40	71	115	600	999	1000
Activated partial thromboplastin time, s	16	5	18	22	135	40	90	150

Critical Limit Survey USA

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Medical Laboratory Observer 2009;August:6-7

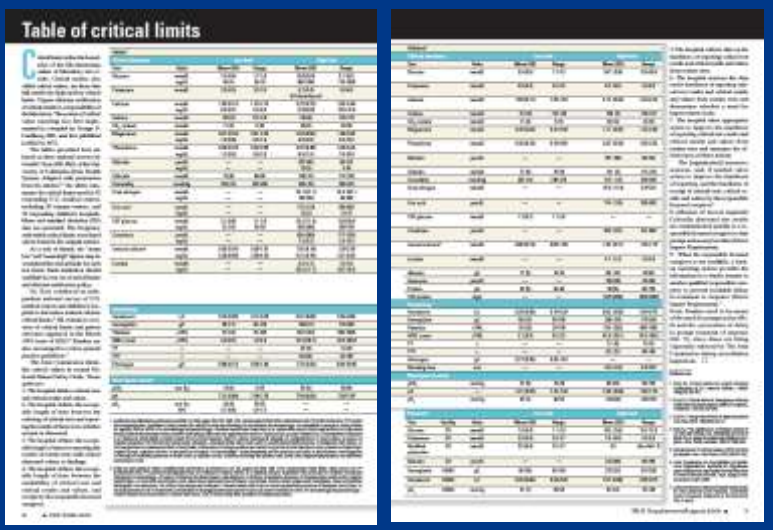
Table of critical limits

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Clin Chem Lab Med 2010;48(4):461–468

Assessment of critical values policies in Italian institutions: comparison with the US situation

Elisa Piva[1], Laura Sciacovelli[1,2], Michael Laposata[3] and Mario Plebani[1,2,*]

Table 2 Comparison of the distribution of critical values. Critical values are ranked according to the 2007 Q-Probes percentile rankings, with the 5th percentile corresponding to the lowest critical values, the 95th percentile corresponding to the highest, and the 50th percentile corresponding to median values.

Critical value	Italian survey			CAP Q-Probes survey		
	5th	50th (median)	95th	5th	50th (median)	95th
Calcium high, mmol/L	2.7	3.2	3.5	3	3.3	3.5
Calcium low, mmol/L	1.4	1.7	2.1	1.5	1.5	1.8
Hemoglobin high, g/L	171	199	200	180	200	230
Hemoglobin low, g/L	50	66	84	50	70	80
Magnesium high, mmol/L	0.93	2	2.9	1.25	2.05	2.9
Magnesium low, mmol/L	0.41	0.5	0.8	0.35	0.4	0.55
Sodium high, mmol/L	150	160	160	150	160	170
Sodium low, mmol/L	110	120	130	110	120	125
Platelet count high, $\times 10^9$/L	449	900	1500	700	999	1000
Platelet count low, $\times 10^9$/L	10	30	85	20	31	70
Activated partial prothrombin time, s	41	85	180	42	80	150

Critical Limit Survey: Italy

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Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art

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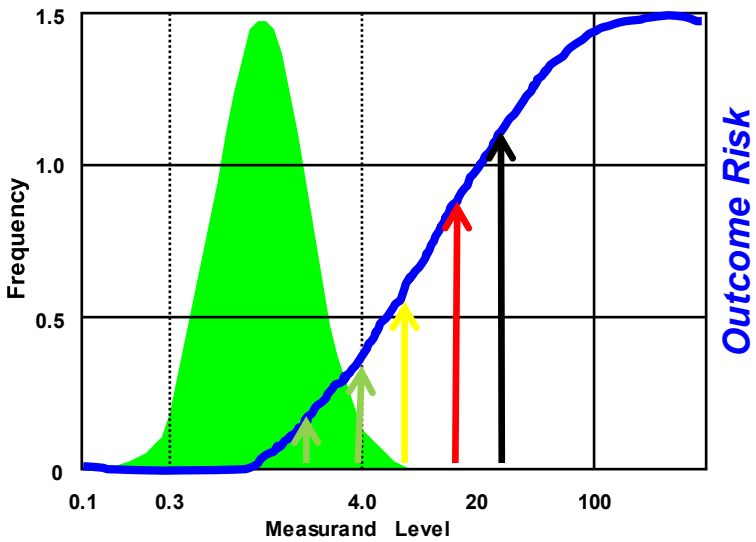

Extremes of Biological Variation

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Abnormal Glucose Frequency

1:1000 Random Glucose > 25.0 mmol/L

Glucose mmol/L	SNP Fasting	Fast EDTA	Fast Serum	SNP Random	Random Serum	AM EDTA	PM EDTA	PM Serum
<7.0	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
7-9.9	1:7	1:11	1:10		1:4	1:7	1:8	1:5
10-11.0	-	1:38	1:38		1:13	1:19	1:24	1:16
11.1-14.9	1:27	1:57	1:58	1:25	1:19	1:27	1:33	1:23
15-19.9	1:120	1:204	1:197	1:71	1:49	1:78	1:79	1:53
20-24.9				1:250	1:169	1:289	1:246	1:132
25-29.9	1:3816	1:6504	1:5300					
30-34.9	1:14055	1:22041	1:23849	1:2109	1:1060	1:2376	1:2073	1:470
35-39.9	1:32015	1:56676	1:23849	1:4385	1:2473	1:7723	1:4405	1:778
>=40	1:57627	1:132244	n/a	1:10142	1:5564	1:10297	1:7047	1:1660

1:1000 Fasting Glucose > 20.0 mmol/L

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Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art

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Sonic Critical Limits


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STANDARDISATION OF CRITICAL VALUES AND NOTIFICATION OF RESULTS

1. *Clinical Outcome*
   (c) Expert Opinions

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Clinical Biochemistry 42 (2009) 766–770

Laboratory defined critical value limits: How do hospital physicians perceive laboratory based critical values?

Andrew C. Don-Wauchope *, Vasudhevan T. Chetty

Table 2
Critical values assessed by the survey showing the current level, the level at which the decision threshold was reached and the proposed change.

Adult critical value	Current level	Response rate %	n	Level at which decision threshold of >60% agree and <20% reject			Proposed level
				Value	% agree	% reject	
Low sodium (mmol/L)	≤120	81	93	≤120	68	9	≤120
High sodium (mmol/L)	≥160	81	93	≥160	79	11	≥160
Low potassium (mmol/L)	≤2.5	79	91	≤2.5	67	12	≤2.5
High potassium (mmol/L)	≥6.0	79	91	≥6.0	61	17	≥6.0
Low ionised calcium (mmol/L)	suggested ≤0.7	70	89	≤0.6	66	18	≤0.6
High ionised calcium (mmol/L)	Not recommended	68	78	data	data	data	Not recommended
Low total calcium (mmol/L)	≤1.5	68	78	≤1.3	76	14	≤1.3
High total calcium (mmol/L)	≥3.5	68	78	≥3.8	68	19	≥3.7

1. *Clinical Outcome*
   (c) Clinician Survey

61-79% clinician agreement

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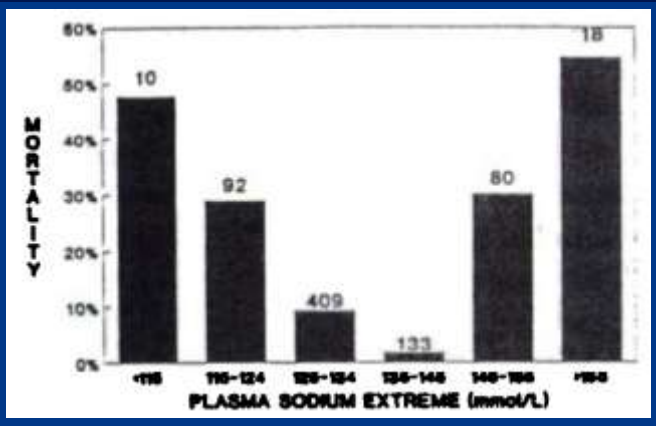
Change in Plasma Sodium Associated with Mortality.

Guerin MD, Martin AL, Sikaris KA, Clin Chem 1992;38:317



1. Clinical Outcome
   (a) Outcome studies

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Q J Med 2009; 102:175–182

Serum sodium as a risk factor for in-hospital mortality in acute unselected general medical patients

B. WHELAN[1], K. BENNETT[2], D. O'RIORDAN[1] and B. SILKE[1,2]

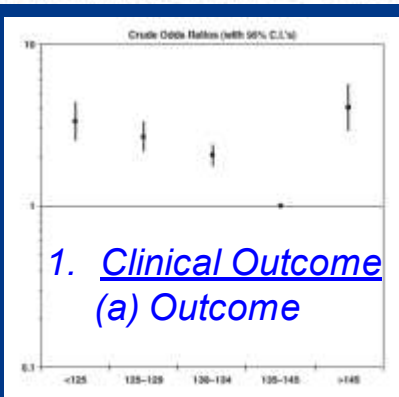

Figure 1. Crude ORs for odds of in hospital mortality in each of the serum sodium groups.

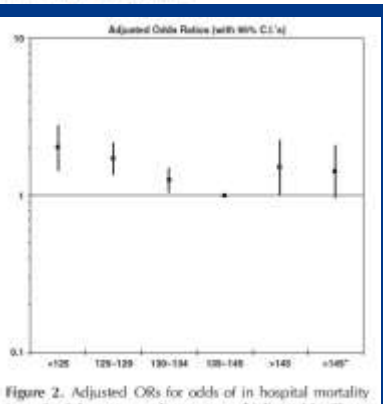

Figure 2. Adjusted ORs for odds of in hospital mortality in each of the serum sodium groups. *Adjusted for Illness Severity Score only.

1. Clinical Outcome
   (a) Outcome

SONIC HEALTHCARE

Sikaris KA, Martin A, Guerin MD, Clin.Biochem.Rev. 1991;12:81

RELATIONSHIP BETWEEN REFERENCE INTERVALS AND MORTALITY-BASED REFERENCE RANGES

K Sikaris, A Martin and MD Guerin

Analyte	Reference Range	Mortality Range*	Critical Range**
Sodium	136-145	133-144	123-148
Potassium	3.5-4.5	3.3-4.6	2.3-5.6
Bicarbonate	22-30	23-36	17-42
Urate	0.2-0.45	>0.79	>0.89
Calcium	2.13-2.63	2.19-2.75	1.89-2.85
Albumin	36-48	<31	<21

* Mortality range is determined by a doubling of mortality over the baseline level.
** Critical range is determined by a 25% mortality rate associated with that analyte level.

1. *Clinical Outcome*
   (a) Outcome

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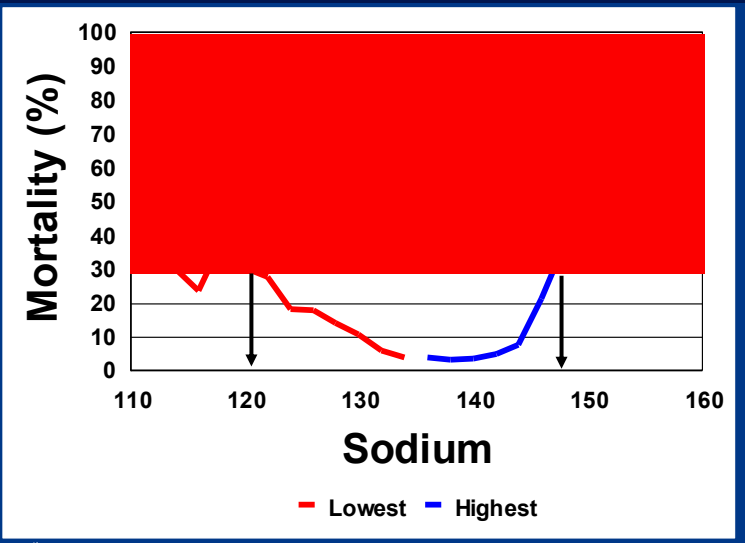
SODIUM & MORTALITY



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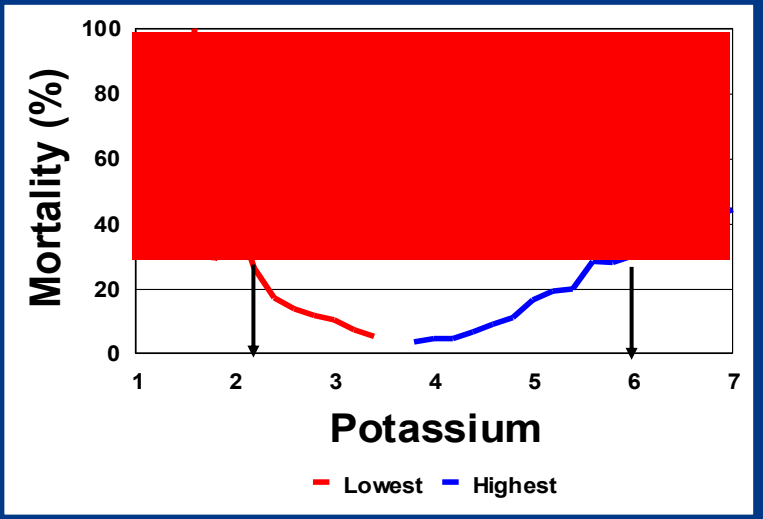
POTASSIUM & MORTALITY



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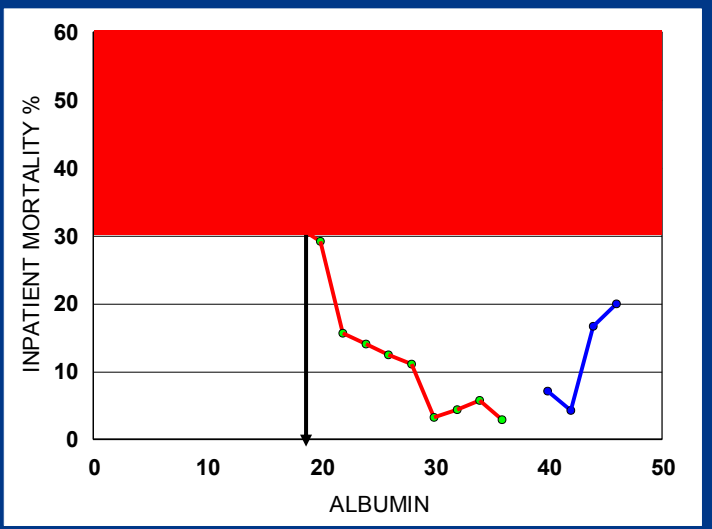
ALBUMIN & MORTALITY



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EFLM

Survey of laboratory 'critical limits'.

Tillman & Barth Ann Clin Biochem 2003;40:181-184.

- Do clinicians respond?
  - Ca^{++}
    - >3.0 mmol/L:
      - immediate change in management
  - Albumin
    - Never changes management
      - (8 labs quote a critical limit)

SONIC HEALTHCARE

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Where are performance criteria relevant?