



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

Performance Criteria for: The Post-analytical Phase

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

A/Prof Ken Sikaris 25th November 2014

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

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10,000 Patients/Day



20,000 Patients/Day

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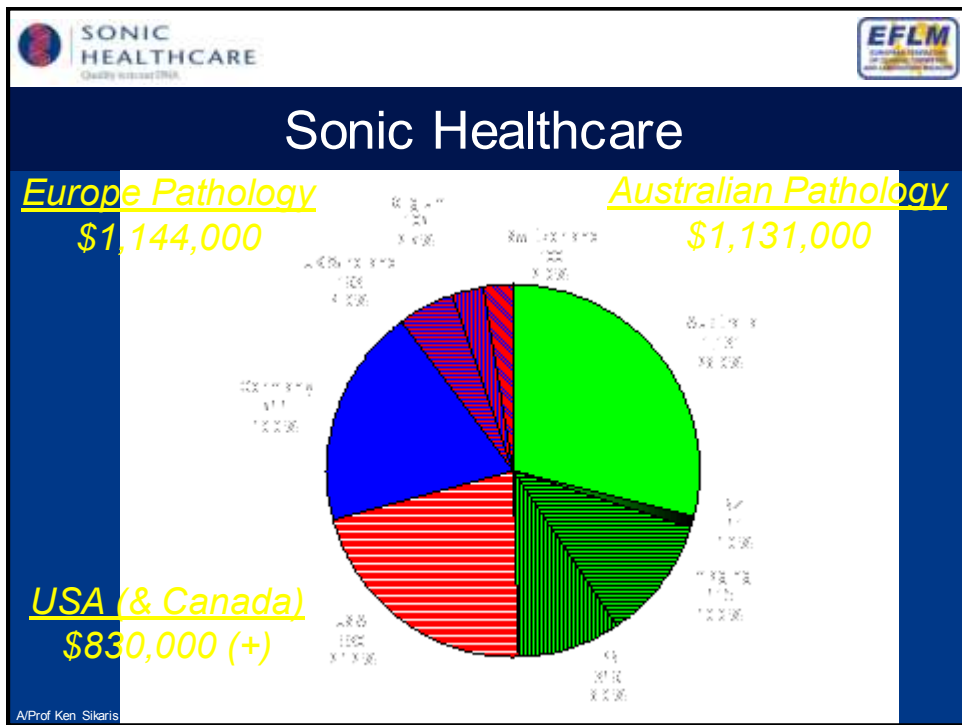
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Sonic Healthcare



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DEFINING PERFORMANCE GOALS

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QUALITY LEVELS: General Concepts

OPTIMUM STANDARD

DESIRABLE

ACCEPTABLE

UNDESIRABLE

MINIMUM STANDARD

UNACCEPTABLE

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Model 3: State of the Art

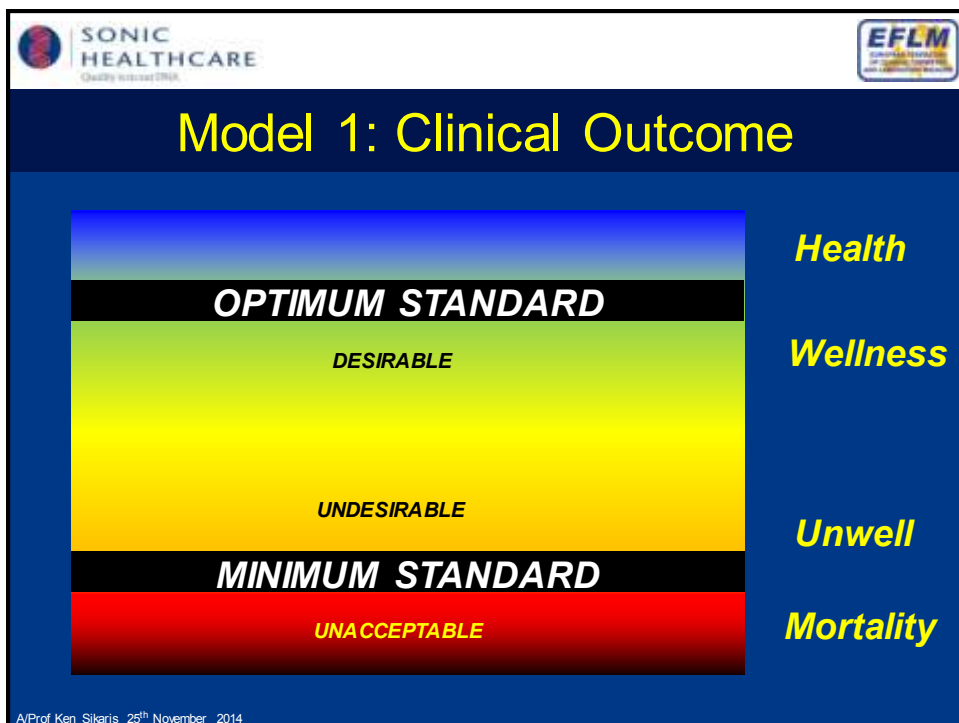
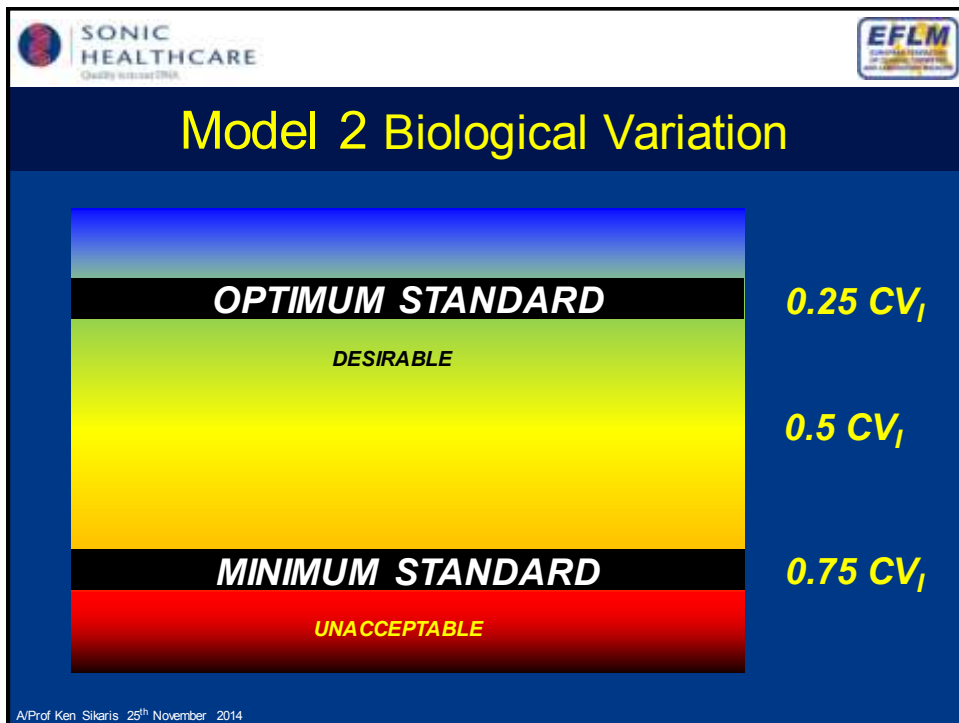
OPTIMUM STANDARD *Best Labs*

ACCEPTABLE *Most Labs*

MINIMUM STANDARD

UNACCEPTABLE *Worst Labs*

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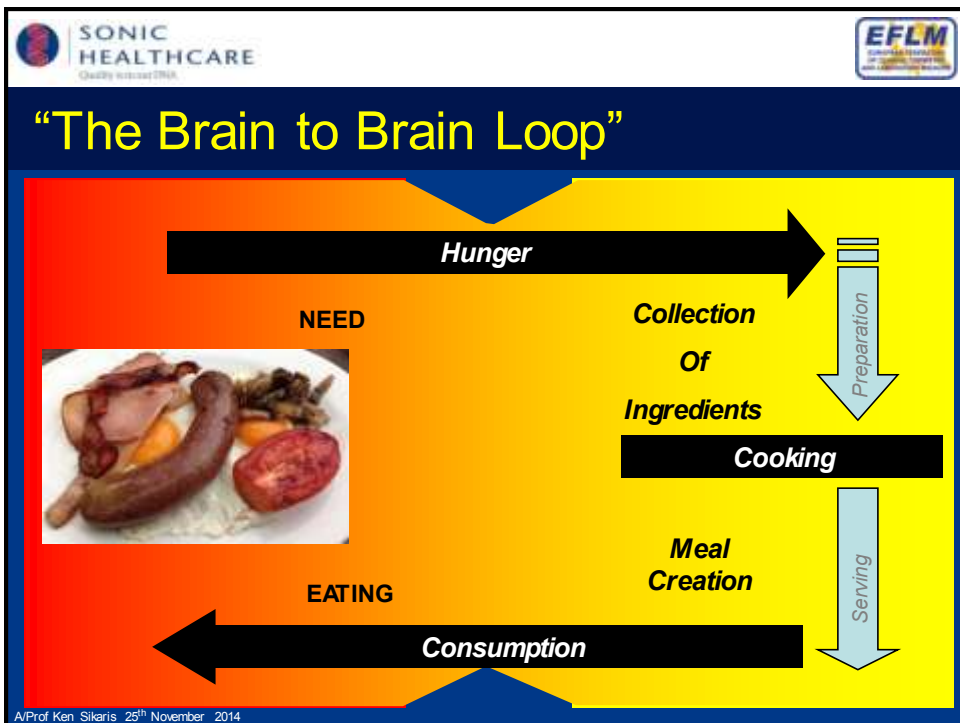


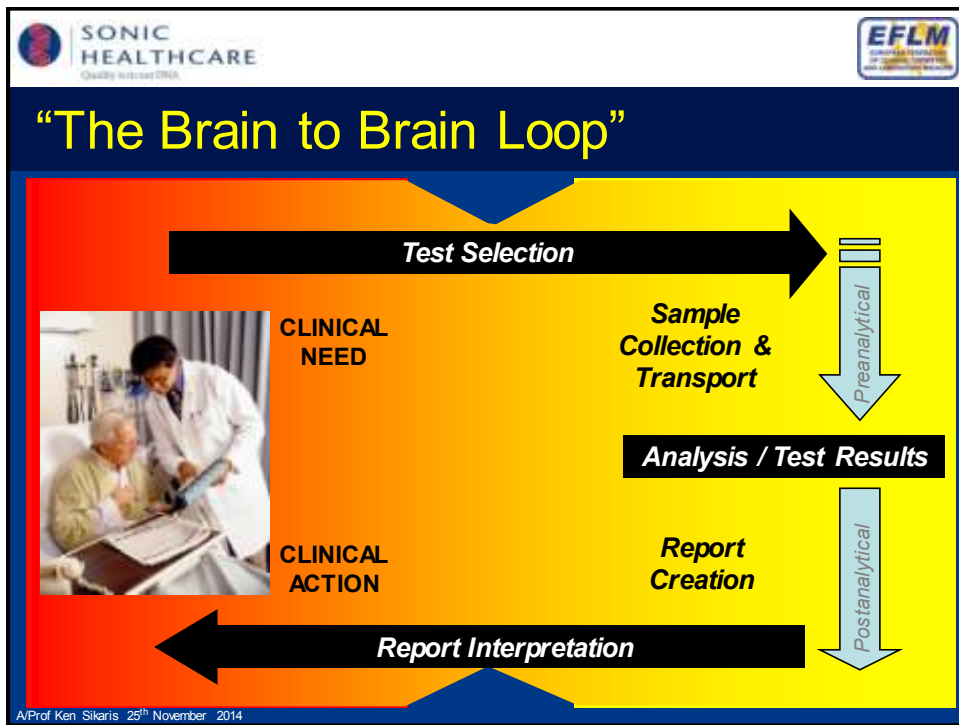
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DEFINING THE POST-ANALYTICAL PHASE

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ISO 17043

Performance Goals:

Defining laboratory proficiency

ISO/IEC 17043

STANDARD

Conformity assessment — General requirements for proficiency testing

Evaluation de la conformité — Exigences générales concernant les essais de Profondeur

General Requirements For Proficiency Testing

ISO IEC

Reference number: ISO/IEC 17043:2010

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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%

Specimen 25-10

Undesirably Low Target Undesirably High

No. of Laboratories

<6.6 7.4 7.9 8.4 >9.2

Normal Control
Very Good Control
Adequate Control
Sub-optimal Control
Poor Control
No Interpretation

Normal
Good
Adequate
Suboptimal
Poor
No Interpretation

No. of Laboratories

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FOR QUALITY IMPROVEMENT

Report Comments: Education/EQA

RCPAQAP
RCPA Quality Assurance Programs

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.
Opioids 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.
Urine/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 75gms 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.nzdiabetes.org.nz). A glucose level of ≥ 9.0 at 1 hour after a 75gms 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;169:83-87.

■ Official Responses (57) Unofficial Responses (39)

Preferred Key Words

No. of Responses

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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

OPTIMUM STANDARD

DESIRABLE

MINIMUM STANDARD

UNAACCEPTABLE

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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

Legend: ■ General practitioners ■ Nurses □ Overall

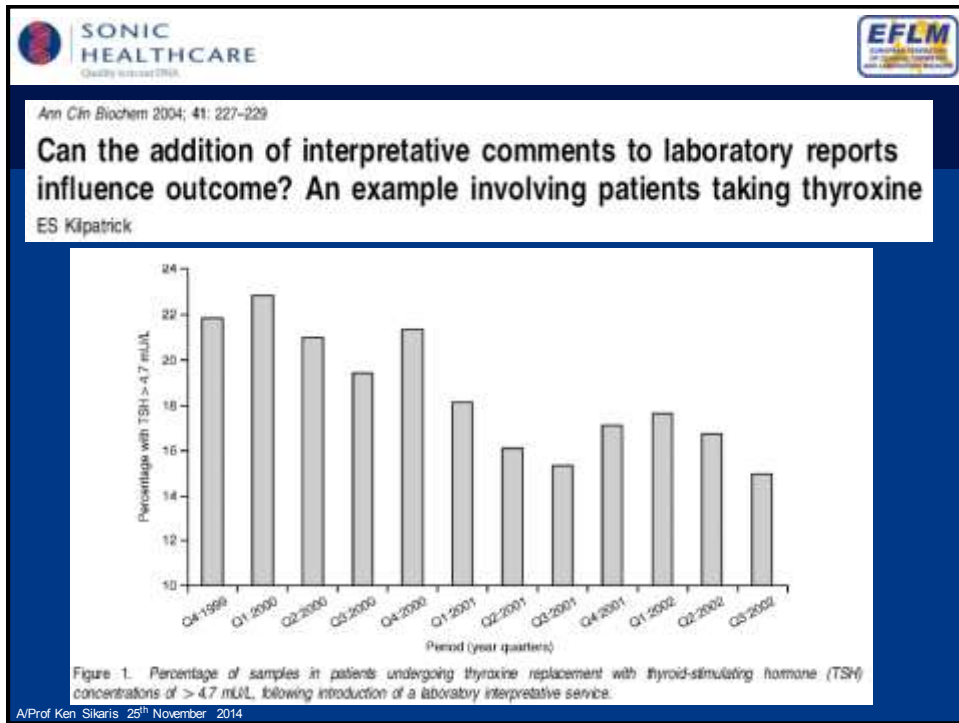
TFT's

Other Hormones

OGTT

Conclusions: Although adding clinical interpretative comments is very time-consuming for senior laboratory staff, there is overwhelming support of the activity among our GPs. Therefore, our local policy of adding clinical comments will remain for the foreseeable future.

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Clinical Chemistry 50:3 632-637 (2004)

Quality Assessment of Interpretative Commenting in Clinical Chemistry

EE MUN LIM,³ KEN A. SIKARIS,^{2,3} JANICE GILL,³ JOHN CALLEJA,³ PETER E. HICKMAN,⁴
JOHN BELBY,^{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.

Case	Key phrases, n			
	Preferred		Less relevant	
	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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Clinical Chemistry 50:3 632-637 (2004)

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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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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. Lai³, Sunil Sethi⁴, Joseph B. Lopez⁵ and Kenneth A. Sikaris⁶

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.

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Ann Clin Biochem 2000; 37: 758–763.

Provision of interpretative comments on biochemical report forms

William J Marshall¹ and Gordon S Challand²

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

Samuel D. Vasikaran^{1,2,*}, Leslie C. Lai³, Sunil Sethi⁴, Joseph B. Lopez⁵ and Kenneth A. Sikaris⁶

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 $\mu\text{g/L}$ 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 cancer 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:

```

graph LR
    DATA[DATA] --> INFORMATION[INFORMATION]
    subgraph CONTEXT
        INFORMATION
    end
    INFORMATION --> KNOWLEDGE(KNOWLEDGE)
    INFORMATION --> HYPOTHESIS(HYPOTHESIS)
    KNOWLEDGE --> DECISION{DECISION}
    HYPOTHESIS --> DECISION
    DECISION --> ACTION[ACTION]
  
```

Pathology: Data Rich, Information Poor?

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

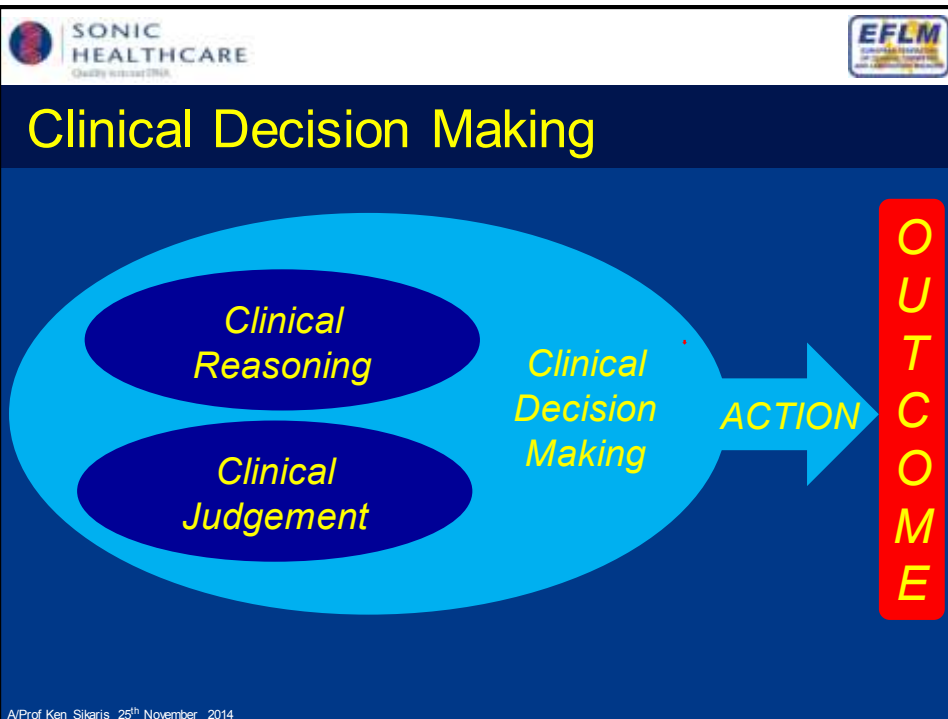
Conceptual Knowledge Acquisition in Biomedicine: A Methodological Review

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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HIERARCHICAL APPROACH TO POST-ANALYTICAL PERFORMANCE CRITERIA

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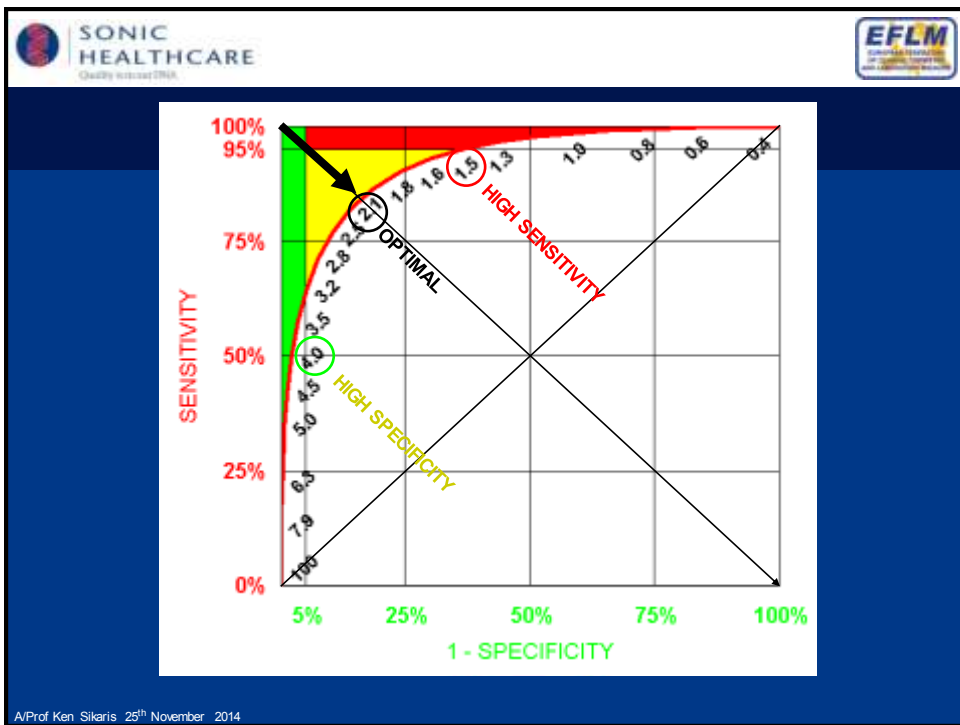
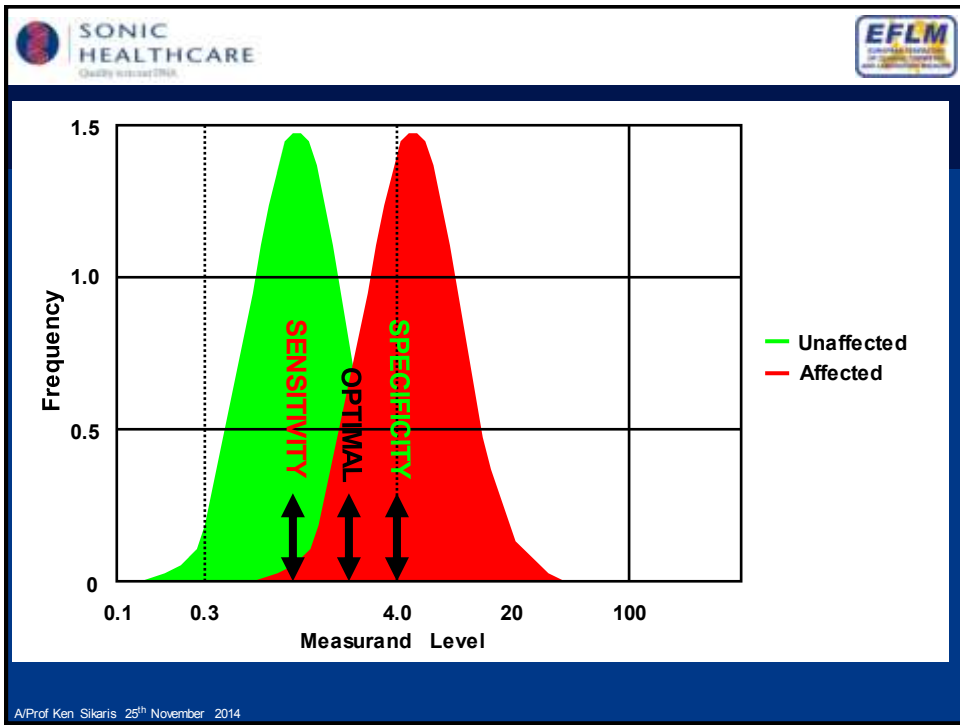



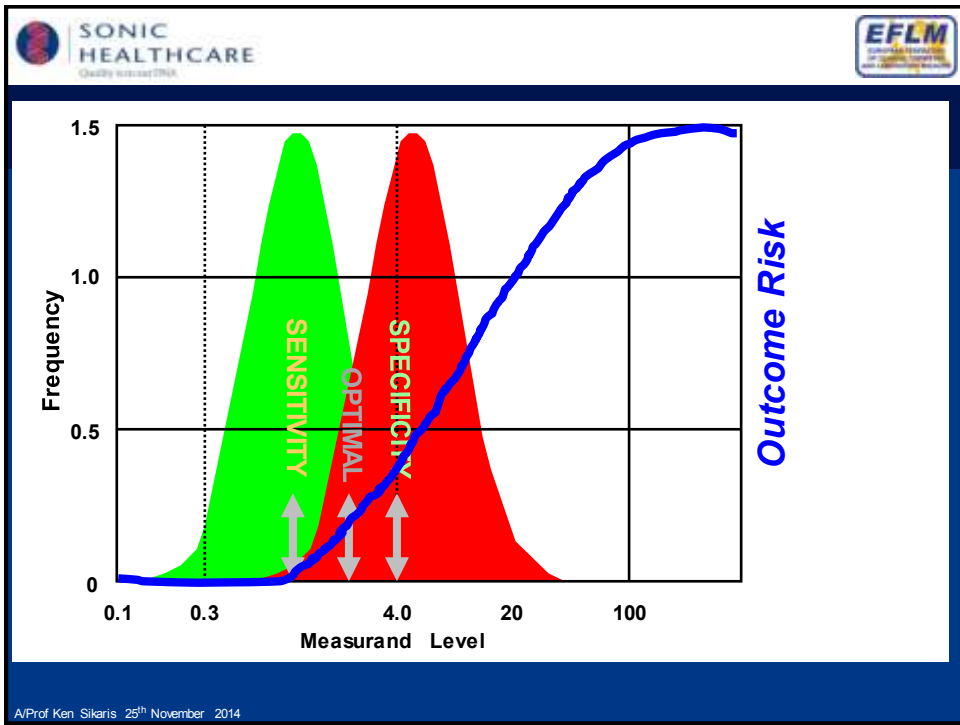
Why reference limits? Why flags?

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	Units
Time	1800	
Lab Id.	91911374	
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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23rd November 2014

AC Milan 1
Inter Milan 1
Crowd 75,000

The slide features the SONIC HEALTHCARE and EFLM logos at the top. The main content is a blue box containing match statistics and two photographs: a wide shot of a stadium at night and a close-up of players celebrating. The text is in yellow and white. A small watermark '© acmilan.com' is visible in the bottom left of the player photo.



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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

IFCC
International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum, Karolinska Institutet
Stockholm April 24-26, 1999

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The Scandinavian Journal of Clinical & Laboratory Investigation

Consensus agreement
U. KERBY, C. G. FRANK, F. HYTIROGLOU, R. A. KALENDER
Department of Clinical Biochemistry, Karolinska Hospital, Stockholm, Sweden; Institute of Biomedical Sciences, University Hospital and Medical School, Aarhus, Denmark; 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 Organizing Committee of the Conference 'Strategies to set Global Quality Specifications in Laboratory Medicine, Stockholm, 24-26 April 1999, are pleased to report that this special Consensus has been accepted. Over 100 participants from 17 countries actively participated in the discussion on the 11 clinical presentations. The primary aim in organizing the Conference was to provide a venue for creating consensus on the setting of global quality specifications in laboratory medicine. This objective was achieved and fully representative debate after the presentations was completed but no agreement on the proposals had been reached in the following Consensus Statement.

CONSENSUS STATEMENT

The main outcome of the Conference was agreement that the following knowledge of needs should be applied to set analytical quality specifications:

1. Evaluation of the effect of medical performance on clinical outcomes in specific clinical settings
2. Evidence of the effect of medical performance on clinical decisions in general
 - a. Data based on comparison of biological variables
 - b. Data based on analysis of reference equations
3. Evidence professional recommendations
 - a. From national and international expert bodies
 - b. From expert level 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 Best From Field or Proficiency Testing schemes
 - b. As found in current publications on methodology

When available, and when appropriate for the medical system, models higher in the hierarchy are to be preferred to those at lower levels. The strategy of such a hierarchy is described in a review published in Clinical Chemistry to which the authors mostly of the above studies are discussed (Clin Chem 1998; 45: 575-8). The hierarchy has also been proposed by the EUROPEAN COLLEGE OF Clinical Chemistry (EFLM) in category 10 'Analytical Performance Goals Based on Medical Needs' in the form of the ongoing revision of ISO 15189:2010. The following studies were also discussed and agreed:

- The above hierarchy includes (nearly) equal weight models; however, new model concepts will undoubtedly emerge. Implementation of any of the models should not risk defined and accepted procedures.
- To facilitate the future setting 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 diagnostic industry and between clinical laboratory professionals and the users of the laboratory service.

ROU, HUPAI and WHO kindly sponsored the Conference but it must be noted that the Consensus Statement reflects the views of the presenters and registrars who participated in the Conference and does not necessarily represent those of the organizing bodies.

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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
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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

Ken Sikaris
Melbourne Pathology, 103 Victoria Parade, Collingwood, Vic. 3066, Australia.
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.⁴¹
 - 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.⁴¹
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.⁴⁸
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.⁵¹
 - b. Current publications on methodology e.g. textbooks or kit inserts.^{54,55}



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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

- [REDACTED]** - investigating the impact of analytical performance of the test on clinical outcomes
- [REDACTED]** - investigating the impact of analytical performance of the test on the probability of clinical outcomes
- [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

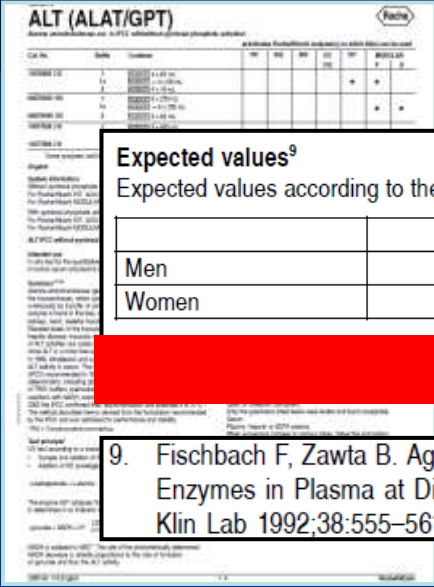
My accreditation experience:

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

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Kit Inserts




Expected values⁹
 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

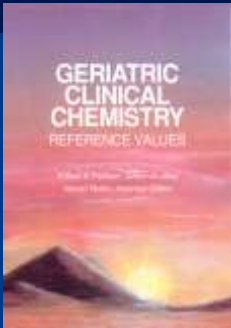
9. Fischbach F, Zawta B. Age-dependent Reference Limits of Several Enzymes in Plasma at Different Measuring Temperatures. *Klin Lab* 1992;38:555-561.


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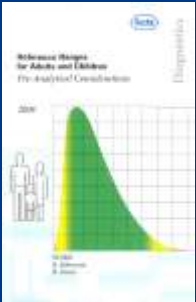



Textbooks











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CLSI C28-A3

C28-A3
1st ed. 06.09
Revised CLSI
1st ed. 09.11


**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.

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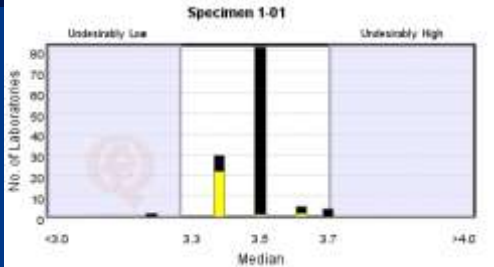


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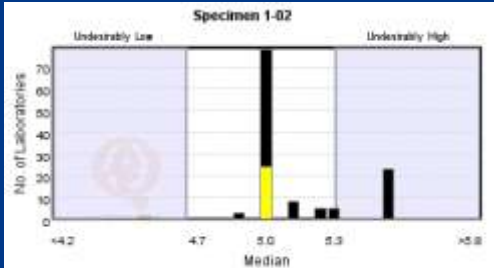
RCPAQAP Survey 2013: Potassium

Vitros Labs

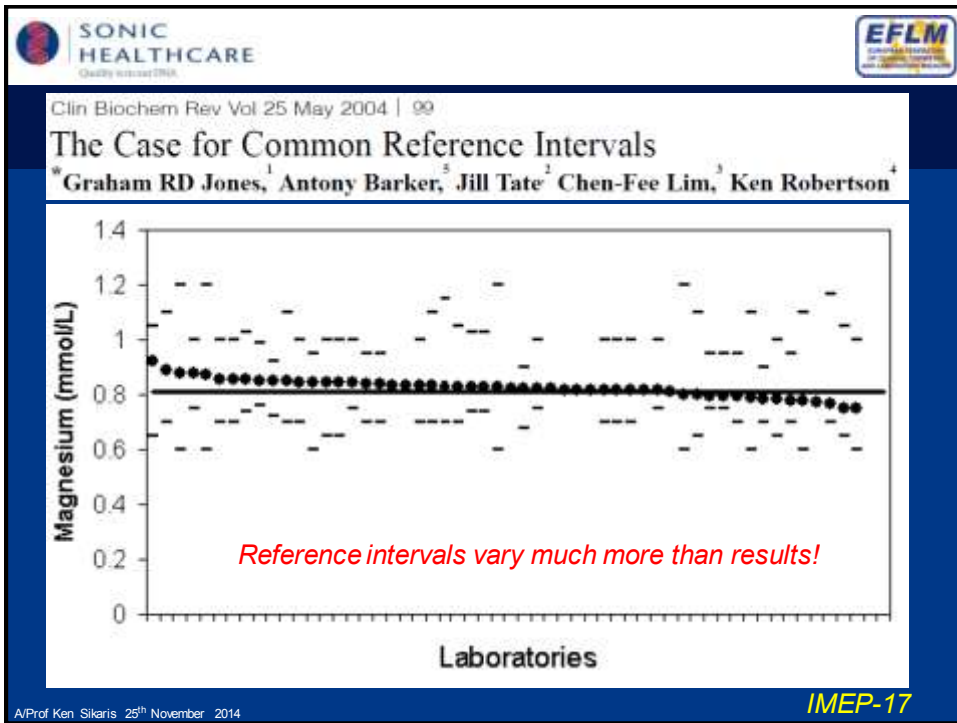


Low

High



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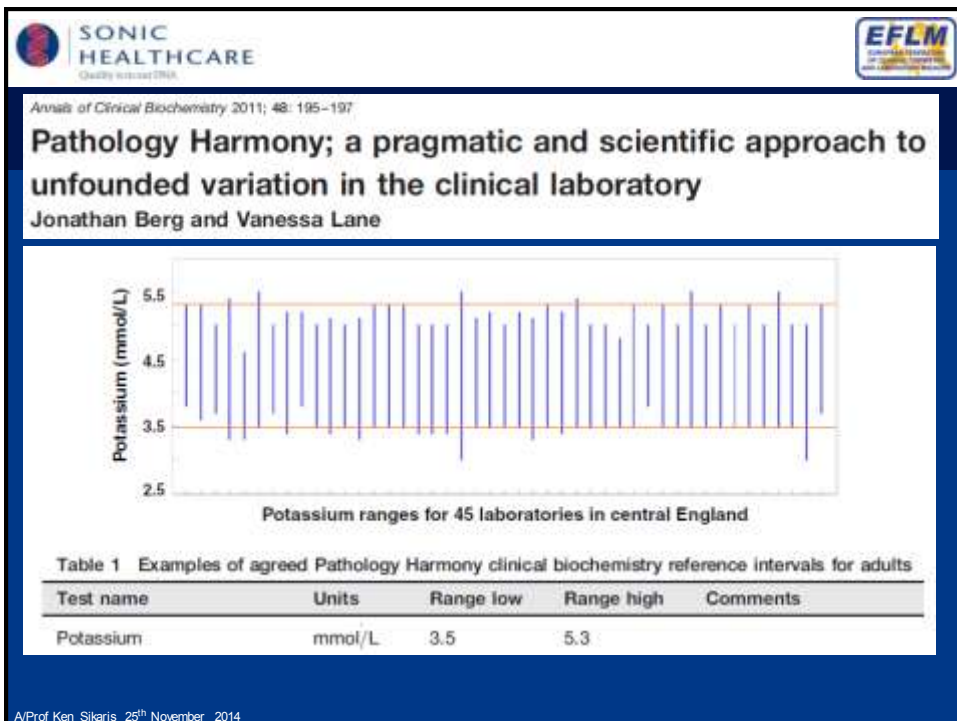
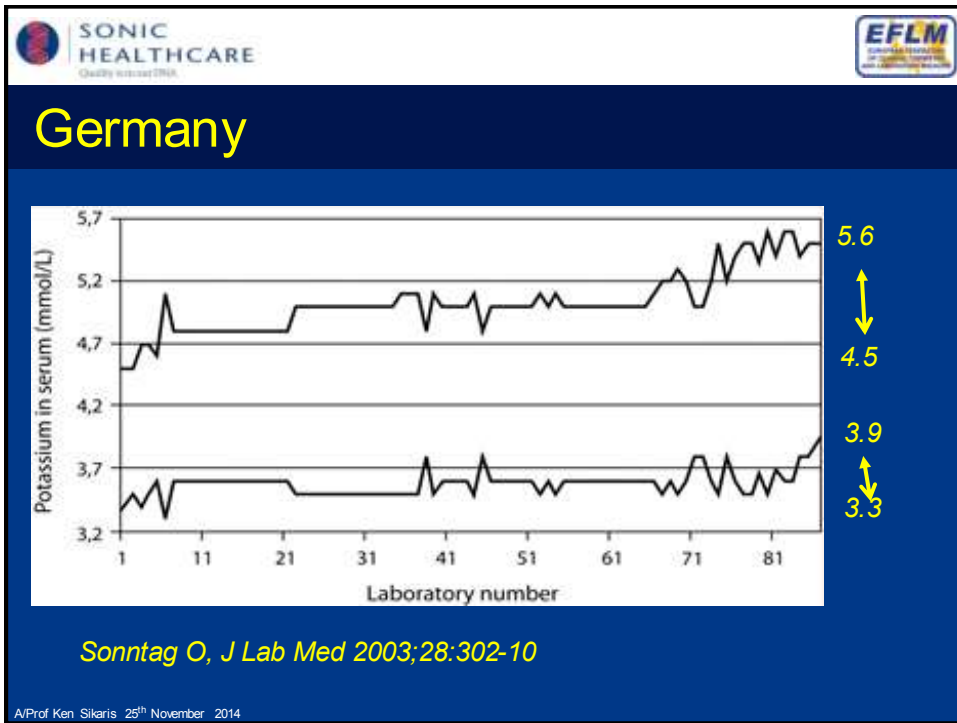
BEYOND ANALYTICAL QUALITY: THE IMPORTANCE OF POSTANALYTICAL QUALITY IN ASSURING CLINICAL VALUE

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)	26.0	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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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, Melles 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 Felding² and Ari Lahti³



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,*}, María Vicenta Doménech² and Carmen Perich³

From Gowans EM, Hytoft 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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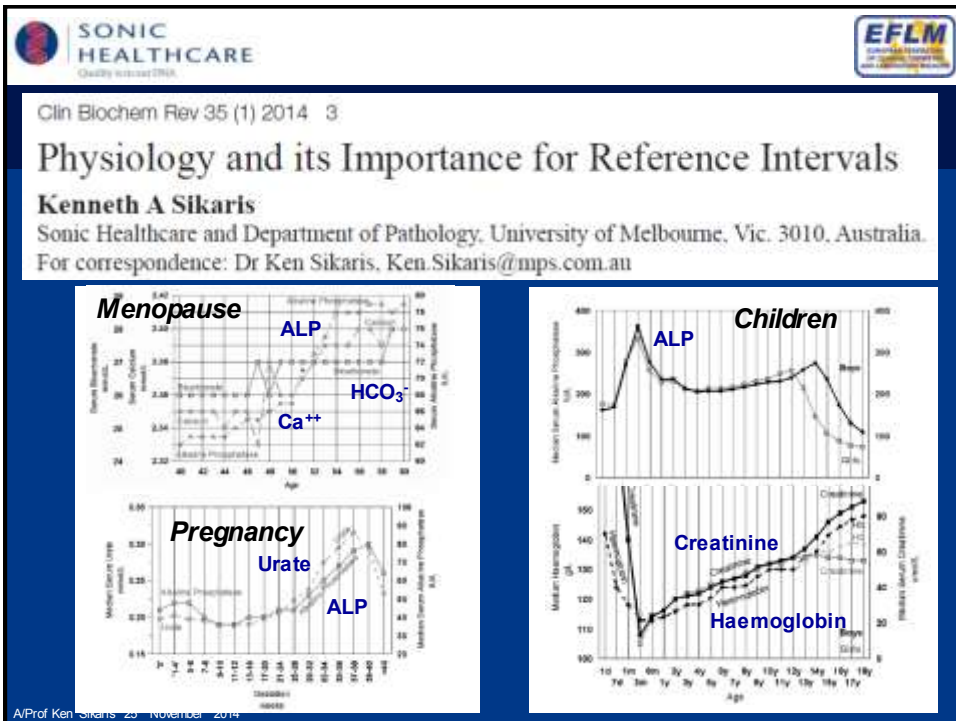



Reference Intervals & Biological Variability

- **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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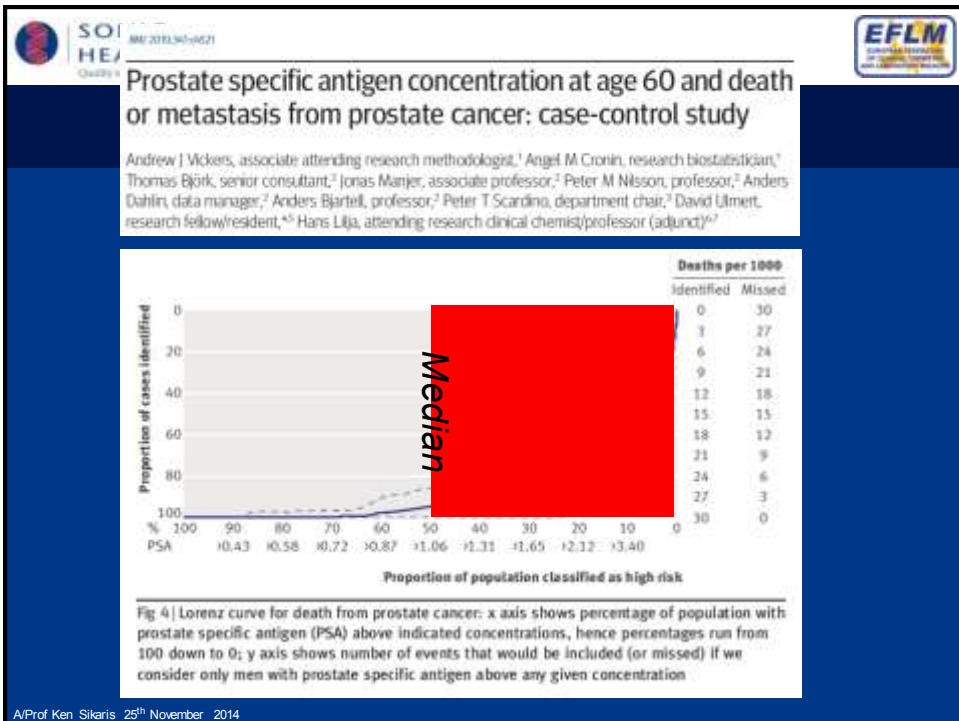
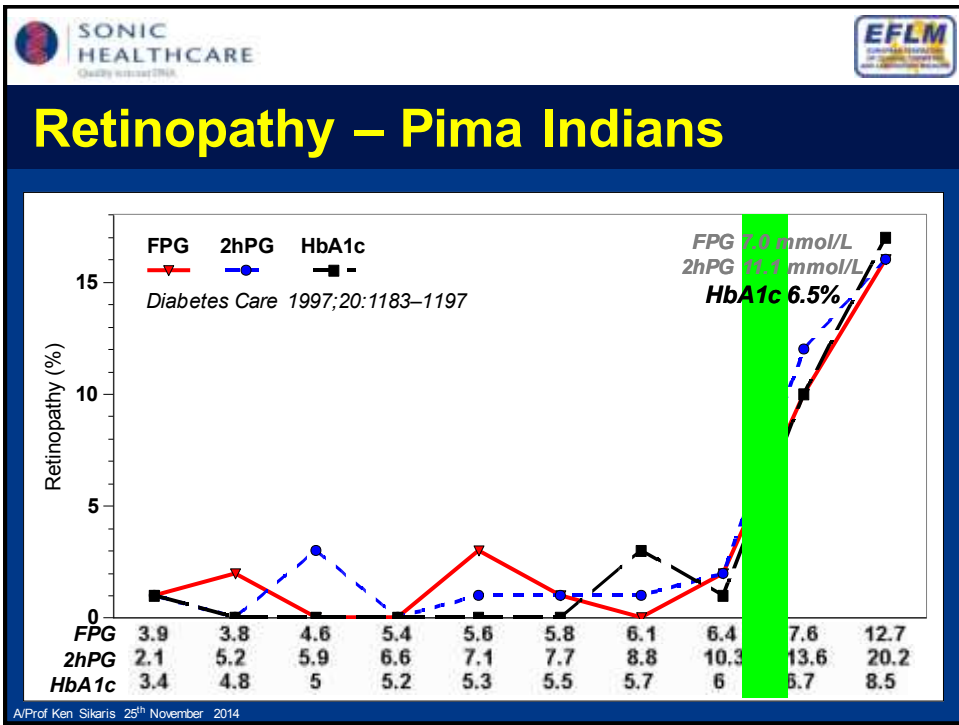
Model 1: Clinical Outcome

- [REDACTED]** - investigating the impact of analytical performance of the test on clinical outcomes
- [REDACTED]** - investigating the impact of analytical performance of the test on the probability of clinical outcomes
- [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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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]

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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^e, Leva Azadi, MPH^f, Alison I. Wilson, MBA^{g,h} and Leah-Anne M. Ruta, PhD^f

Table 1. Summary of Recommendations.

Recommendation	Grade
<i>Investigations: serum troponin measurement</i>	
Where available, high sensitivity troponin assays should be used in preference to conventional assays.	N/A
When using high sensitivity troponin assays, 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

Figure 1. Incidence of Cardiovascular Death According to Quartile of High-Sensitivity Cardiac Troponin T Level.

Cumulative Incidence of Cardiovascular Death (%)

Months

High-sensitivity cardiac troponin T levels (µg/liter)

	Q1	Q2	Q3	Q4
Men	≤0.0042	0.0043–0.0062	0.0063–0.0095	≥0.0096
Women	≤0.0027	0.0028–0.0045	0.0046–0.0073	≥0.0074

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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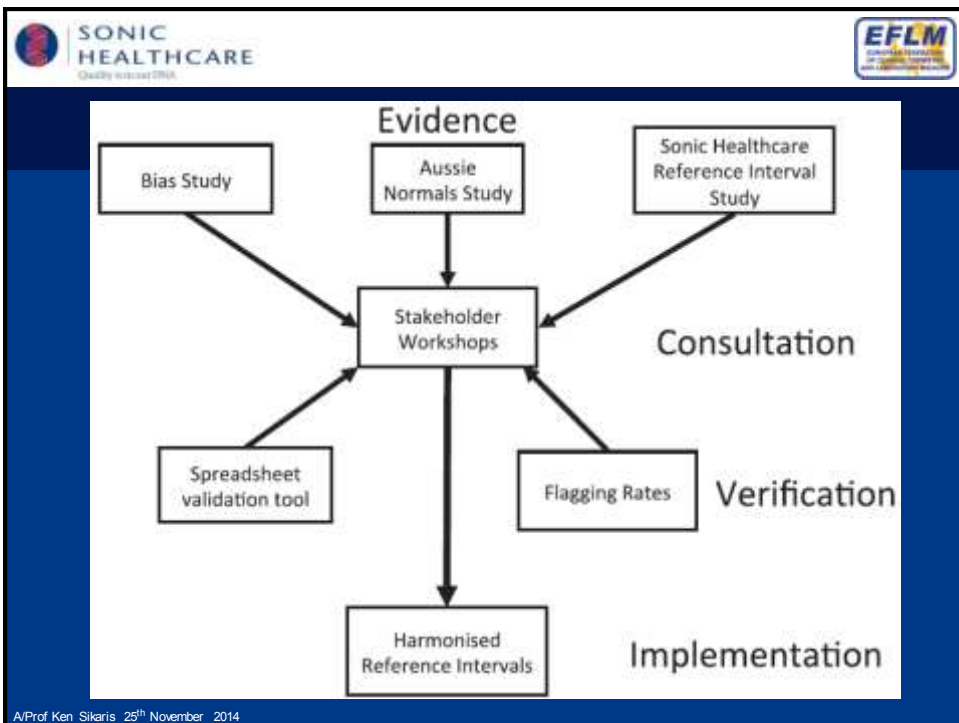
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AACB Harmonised Reference Interval Consensus




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Australian reference intervals in healthy adults (ARIA) study



Introduction

Reference intervals (RIs) are essential for the accurate interpretation of laboratory test results. Defining reference intervals (RIs) is a "challenging" process and these often a "classical" category. The ARIA study was a collaborative effort between the Royal Australian College of General Practitioners (RACGP) and the Royal Australian College of Pathologists (RACP) to determine reference intervals (RIs) for healthy adult Australians. All outcomes made in the laboratory region participate completed a questionnaire that included questions associated with lifestyle factors such as: diet, exercise and smoking. Lifestyle was not included in the reference interval calculation. The study included 10,000 healthy adults aged 18 to 80 years. The study included 10,000 healthy adults aged 18 to 80 years. The study included 10,000 healthy adults aged 18 to 80 years.

Materials and Methods

10000 laboratory samples were collected into gel separation reference tubes containing no anticoagulant and were analysed within 2 hours of collection. Plasma analyte concentrations were measured on a Hitachi 7090 analyser with each result stored as a PDF file for analysis for the reference interval. Up to 40 individual samples were undertaken on the Abbott ARCHITECT iSTAT/STAT analyser for each patient's laboratory reference interval and reference interval. Results were partitioned based on gender and age (18-24, 25-44, 45-64, 65-80 years) and gender and age. Parameters were not included in the analysis if they were not included in the reference interval and reference interval.


Results

Reference intervals are given in Table 1. The results presented in this study comply with the WHO's laboratory accreditation requirements and the WHO's reference interval requirements. There are some differences seen in both the WHO's (Table 1) and (2) study also shows both gender and age differences in Table 1 and Table 2. The results also are also consistent with those reported in commonly accepted and published reference intervals by the Royal Australian College of General Practitioners (RACGP) and the Royal Australian College of Pathologists (RACP).


Table 1. Comparison between ARIA study and suggested AACB working party reference intervals. *SQT (Squat & New Adult's Diagnostic Committee) for Male (M), Female (F)

Analyte	ARIA (Adult)	Suggested AACB Reference Interval
Na	135 - 144	135 - 145
K	3.6 - 4.9	3.5 - 5.0
Cl	100 - 108	100 - 109
CO2	20 - 29	20 - 29
Urea		2.5 - 7.0
Urea <60 Y	4.0 - 9.1	2.5 - 7.0
Urea >60 Y	3.9 - 8.8	2.5 - 7.0
Creatinine	4.2 - 9.3	2.5 - 7.0
ALT	65 - 107	56 - 88
AST	12 - 59	8 - 43
ALP	14 - 47	13 - 37
GGT (New)*	39 - 111	12 - 71
CK	46 - 295	8 - 35
LD (L-P)	124 - 232	46 - 295
Tot. Protein	62 - 78	37 - 250
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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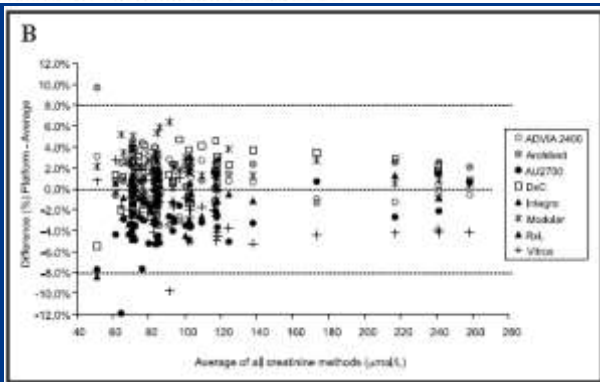
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Clin Biochem Rev 35 (4) 2014 213

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,¹ Graham RD Jones,² 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 μ mol/L	45 – 90 μ mol/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, Meliss S, editors. Geriatric clinical chemistry reference values. AACC Press: Washington, DC, 1994:p44.

Significant Change: Biological

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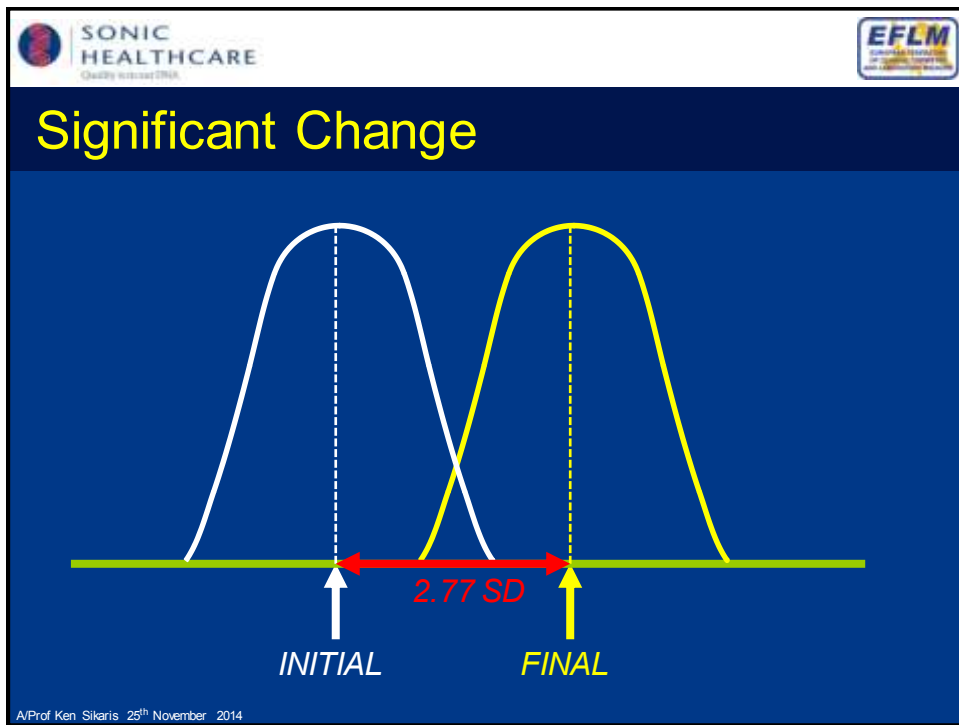
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Post-analytical: Significant Change

- Clinical Outcome
- Biological Variation
- State of the Art

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Significant Change: Biological Variability

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

Significant Change: Biological

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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^e, Philip A. Tideman, FRACP^d, Jill Waddell, MPH^f, Leva Azadi, MPH^f, Alison I. Wilson, MBA^{g,h} and Leah-Anne M. Ruta, PhD^f

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When using high sensitivity troponin assay, a test should be interpreted as positive if level is ≥ 99 th centile for reference population OR [redacted] 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

AP

Change in Plasma Sodium Associated with Mortality.

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

Change in Plasma Sodium Associated with Mortality

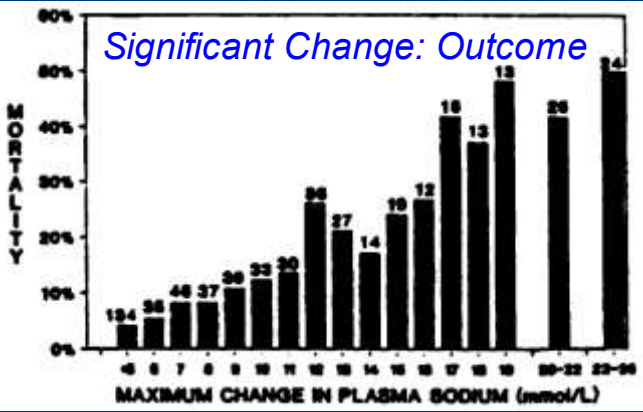
By the Editor:

Hypernatremia, as defined by a serum concentration of sodium of greater than 152 mmol/L, is one of the most common electrolyte abnormalities in hospitalized patients (1) in a 12-month period involving 1000 inpatients of our hospital. 40% (400) were found to have at least one episode of hypernatremia.

After the development of a coronary revascularization program at a tertiary care center (University of California, San Francisco, CA, Fresno, CA), the implementation of a protocol (2) to manage hypernatremia (3) in the coronary care unit (CCU) and intensive care unit (ICU) and the development of a unit of the hospital have been reported (4). In addition to the data reported by Guerin and Cooper (5), these authors found a mortality rate of 34% in patients who had hypernatremia (serum sodium ≥ 152 mmol/L) at presentation to the intensive care unit (ICU) and a mortality rate of 26% in patients who had hypernatremia (serum sodium ≥ 152 mmol/L) at admission to the CCU. In addition, we report that in a study involving 1000 inpatients, of whom the majority were hospitalized in the CCU, the mortality rate was 26%.

Using another cohort study, we have shown that the mortality rate is higher in patients who develop hypernatremia during their hospital stay than in patients who do not develop hypernatremia during their hospital stay (6).

A further study was performed to determine mortality with the maximum change in plasma sodium during an admission period (Figure 1). Using this change of plasma sodium reported to us during an admission, there appeared to be an almost linear increase in mortality with increasing maximum change in plasma sodium.



Maximum Change in Plasma Sodium (mmol/L)	Mortality (%)
4-5	13
6	14
7	14
8	14
9	14
10	14
11	14
12	14
13	14
14	14
15	14
16	14
17	14
18	14
19	14
20	14
21-22	26
23-24	34

Significant Change: Outcome

References
1. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.
2. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.
3. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.
4. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.
5. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.
6. Guerin MD, Cooper DJ. Hypernatremia. *Clin Chem* 1992;38:317-21.

Michael D. Guerin, MD, PhD, University of California, San Francisco, CA
Alan L. Martin, MD, University of California, San Francisco, CA
Ken Sikaris, MD, University of California, San Francisco, CA

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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.

Freedom from clinical progression

Years from first BCCA appointment

PSA static / falling

PSAdt > 3 years

PSAdt 18 mo - 3 years

PSAdt < 18 months

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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ANALYTICAL QUALITY ASSURANCE
AND STANDARDIZATION

When to panic over an abnormal result.

George D Lundberg, Med Lab Obs 1972;

CRITICAL VALUES REPORTED IN ONE WEEK OF SEPTEMBER 1971			
TEST	LOW CRITICAL VALUE	HIGH CRITICAL VALUE	TOTAL TESTS PERFORMED
Serum sodium	9	None	4,527
Serum potassium	13	21	4,173
Serum potassium—Potassium	None	1	4,173
Serum potassium—Ionized potassium	None	9	4,173
Serum glucose	18	17	4,838
Serum glucose—Hexokinase	None	7	4,838
Serum calcium	None	None	588
Prothrombin activity	21	None	1,212
Arterial or capillary blood pH	7.25	None	275
Arterial or capillary blood pCO ₂	7	25	275
Arterial or capillary blood pH	7.25	None	275
Serum bicarbonate	17	18	4,891
Platelet count	1	None	176
Partial FBC volume	4	None	5,274
Blood hemoglobin	6	None	5,274
Positive blood culture (31)			572
Positive cerebrospinal fluid gram stain (5)			216

PANIC VALUES			
TEST	LOW	HIGH	CRITICAL VALUE
Serum sodium	< 120 mEq/L	> 160 mEq/L	> 170 mEq/L
Serum potassium	< 2.5 mEq/L	> 6.5 mEq/L	> 7.0 mEq/L
Serum glucose	< 2.0 mmol/L	> 10.0 mmol/L	> 12.0 mmol/L
Serum potassium—Ionized potassium	< 1.0 mmol/L	> 3.0 mmol/L	> 3.5 mmol/L
Serum glucose	< 2.0 mmol/L	> 10.0 mmol/L	> 12.0 mmol/L
Serum glucose—Hexokinase	< 2.0 mmol/L	> 10.0 mmol/L	> 12.0 mmol/L
Serum calcium	< 1.0 mmol/L	> 3.0 mmol/L	> 3.5 mmol/L
Prothrombin activity	< 20%	> 100%	> 120%
Arterial or capillary blood pH	< 7.25	> 7.45	> 7.55
Arterial or capillary blood pCO ₂	< 7	> 25	> 30
Serum bicarbonate	< 15	> 25	> 30
Platelet count	< 100,000	> 1,000,000	> 1,200,000
Partial FBC volume	< 4	> 10	> 12
Blood hemoglobin	< 6	> 18	> 20
Positive blood culture			> 1
Positive cerebrospinal fluid gram stain			> 1

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ANALYTICAL QUALITY ASSURANCE
AND STANDARDIZATION

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. Wagat, MD, FCAP; Richard C. Friedberg, MD, PhD, FCAP; Rhona Souws, MS; Ana K. Stankovic, MD, PhD, FCAP

Table 4. Adult and Pediatric Median Critical Values

Analyte	No. of Institutions	Low Critical Value Percentiles			No. of Institutions	High Critical Value Percentiles		
		5th	50th (Median)	95th		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, $\times 10^9/\mu\text{L}$	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	6.5
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	141	5.0	7.0	8.1	98	18.0	20.0	25.0
Hemoglobin, female patients, g/dL	141	5.0	7.0	8.1	99	18.0	20.0	25.0
Platelet count, $\times 10^9/\mu\text{L}$	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

(Note: The table contains two columns of data, each with multiple rows of test names and their corresponding critical limits. The text is small and partially obscured by the image quality.)

Clin Chem Lab Med 2010;48(4):461-468

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

Elisa Piva¹, Laura Sciacovelli^{1,2}, Michael Laposata³ 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, ×10 ⁹ /L	449	900	1500	700	999	1000
Platelet count low, ×10 ⁹ /L	10	30	85	20	31	70
Activated partial prothrombin time, s	41	85	180	42	80	150

Critical Limit Survey: Italy

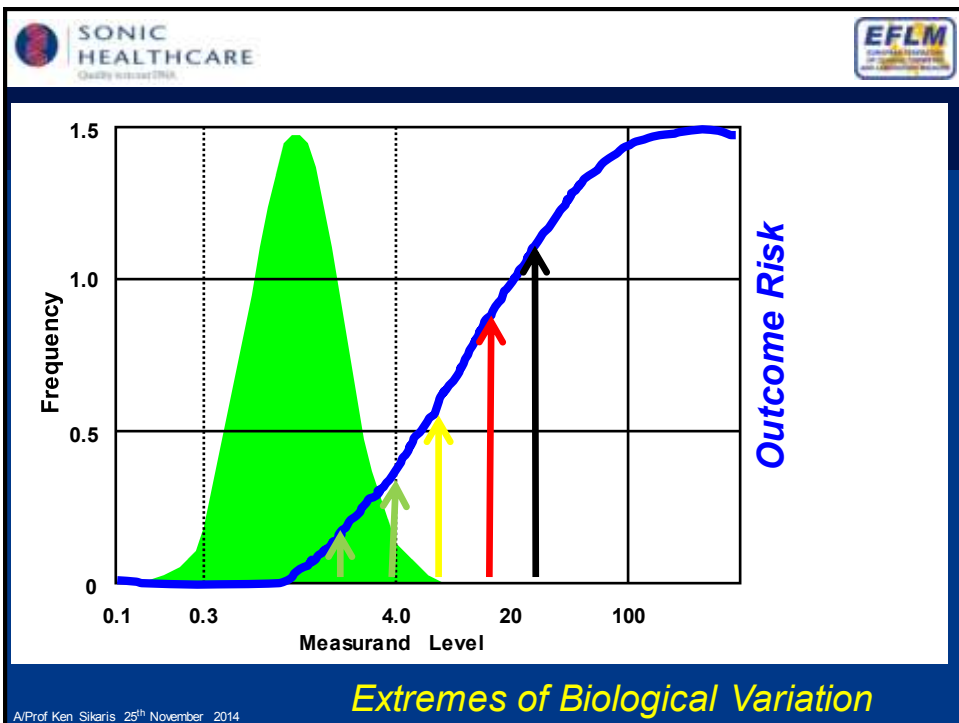
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Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art

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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

STANDARDISATION OF CRITICAL VALUES AND NOTIFICATION OF RESULTS

A. Kinnear, G. Ainsworth, G. Ward, J. Brown, G. Callaway, F. Hain, M. Taylor, K. Jay, J. Beithman, G. Brown, K. Skene, J. J. B. Sinden, M. Skene, J. D. Jay

OBJECTIVE
List of values are used to identify patients at risk who require the prompt attention of a specialist. This document provides a list of values which are used to identify patients at risk who require the prompt attention of a specialist. This document provides a list of values which are used to identify patients at risk who require the prompt attention of a specialist.

SCOPE
This document applies to all patients who are admitted to hospital. It applies to all patients who are admitted to hospital. It applies to all patients who are admitted to hospital.

RESULTS
The list of values is used to identify patients at risk who require the prompt attention of a specialist. It is used to identify patients at risk who require the prompt attention of a specialist. It is used to identify patients at risk who require the prompt attention of a specialist.

CONCLUSIONS
The list of values is used to identify patients at risk who require the prompt attention of a specialist. It is used to identify patients at risk who require the prompt attention of a specialist. It is used to identify patients at risk who require the prompt attention of a specialist.

REFERENCES
1. ...
2. ...
3. ...

Sonic Healthcare Medical Critical Value List (12/14)

Parameter	Current Level	Proposed Level	Response	Notification
Na ⁺	135-145 mmol/L	135-145 mmol/L	Urgent	Urgent
K ⁺	3.5-5.5 mmol/L	3.5-5.5 mmol/L	Urgent	Urgent
Ca ²⁺	2.0-2.6 mmol/L	2.0-2.6 mmol/L	Urgent	Urgent
Mg ²⁺	0.8-1.2 mmol/L	0.8-1.2 mmol/L	Urgent	Urgent
Cl ⁻	98-108 mmol/L	98-108 mmol/L	Urgent	Urgent
BUN	3.0-10.0 mmol/L	3.0-10.0 mmol/L	Urgent	Urgent
Cr	0.6-1.3 mg/dL	0.6-1.3 mg/dL	Urgent	Urgent
Glucose	3.9-6.3 mmol/L	3.9-6.3 mmol/L	Urgent	Urgent
HbA1c	4.0-6.0 %	4.0-6.0 %	Urgent	Urgent
INR	0.8-1.2	0.8-1.2	Urgent	Urgent
aPTT	25-35 sec	25-35 sec	Urgent	Urgent
Fibrinogen	2-4 g/L	2-4 g/L	Urgent	Urgent
D-dimer	<0.5 mg/L	<0.5 mg/L	Urgent	Urgent
Troponin I	<0.1 ng/mL	<0.1 ng/mL	Urgent	Urgent
Troponin T	<0.05 ng/mL	<0.05 ng/mL	Urgent	Urgent
CK-MB	<5 U/L	<5 U/L	Urgent	Urgent
CK	<100 U/L	<100 U/L	Urgent	Urgent
LDH	<250 U/L	<250 U/L	Urgent	Urgent
AST	<40 U/L	<40 U/L	Urgent	Urgent
ALT	<40 U/L	<40 U/L	Urgent	Urgent
Amylase	<100 U/L	<100 U/L	Urgent	Urgent
Lipase	<100 U/L	<100 U/L	Urgent	Urgent
Urea	2.5-7.5 mmol/L	2.5-7.5 mmol/L	Urgent	Urgent
Creatinine	0.6-1.3 mg/dL	0.6-1.3 mg/dL	Urgent	Urgent
Uric acid	3.5-7.0 mg/dL	3.5-7.0 mg/dL	Urgent	Urgent
Alkaline Phosphatase	40-120 U/L	40-120 U/L	Urgent	Urgent
Gamma-GT	<30 U/L	<30 U/L	Urgent	Urgent
Bilirubin	<1.2 mg/dL	<1.2 mg/dL	Urgent	Urgent
Aspartate Aminotransferase	<40 U/L	<40 U/L	Urgent	Urgent
Alanine Aminotransferase	<40 U/L	<40 U/L	Urgent	Urgent
Lactate	<2.0 mmol/L	<2.0 mmol/L	Urgent	Urgent
Prothrombin Time	11-14 sec	11-14 sec	Urgent	Urgent
Partial Thromboplastin Time	25-35 sec	25-35 sec	Urgent	Urgent
Fibrinogen	2-4 g/L	2-4 g/L	Urgent	Urgent
D-dimer	<0.5 mg/L	<0.5 mg/L	Urgent	Urgent
Urea Nitrogen	2.5-7.5 mg/dL	2.5-7.5 mg/dL	Urgent	Urgent
Creatinine	0.6-1.3 mg/dL	0.6-1.3 mg/dL	Urgent	Urgent
Glucose	3.9-6.3 mmol/L	3.9-6.3 mmol/L	Urgent	Urgent
Electrolytes	As above	As above	Urgent	Urgent

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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 >66% 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 ≤1.7	70	80	≤0.6	66 / 18	≤0.6
High ionised calcium (mmol/L)	Not recommended	68	78	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

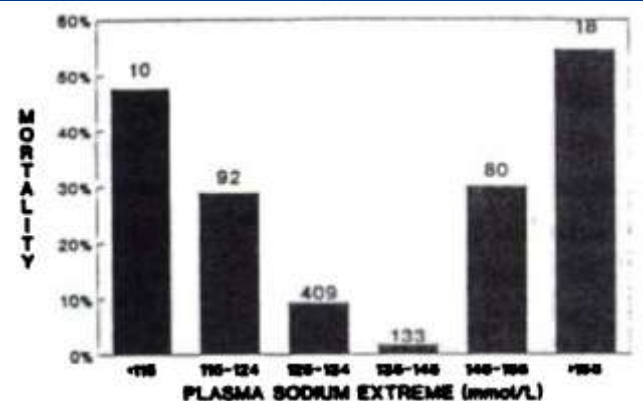
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Change in Plasma Sodium Associated with Mortality.

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



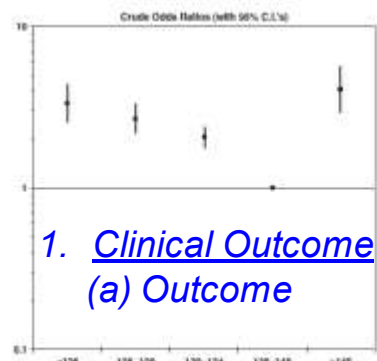
Plasma Sodium Extreme (mmol/L)	Mortality (%)
<116	~55
116-124	~30
126-134	~10
136-146	~5
146-156	~30
>156	~55

1. Clinical Outcome
(a) Outcome studies

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

B. WHELAN¹, K. BENNETT², D. O'RIORDAN¹ and B. SILKE^{1,2}



1. Clinical Outcome
(a) Outcome

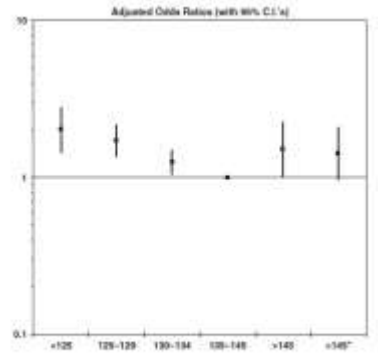


Figure 1. Crude ORs for odds of in hospital mortality in each of the serum sodium groups.

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

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

RELATIONSHIP BETWEEN REFERENCE INTERVALS AND MORTALITY-BASED REFERENCE RANGES

S. Sikaris, A. Martin and MD Guerin
Department of Chemical Pathology, Heidelberg Repatriation Hospital, Private Bag No. 1, Heidelberg West, VIC 3101.

There have been many attempts to define health ranges for clinical laboratory analyses, including normal ranges and reference ranges. There have been fewer attempts, however, to link changes in analyte levels in healthy individuals with clinical decision levels. Clinical decision levels, however, may be linked with mortality associated with a pathological change.

A 24-month study in normal mortality and the currently accepted for several years.

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

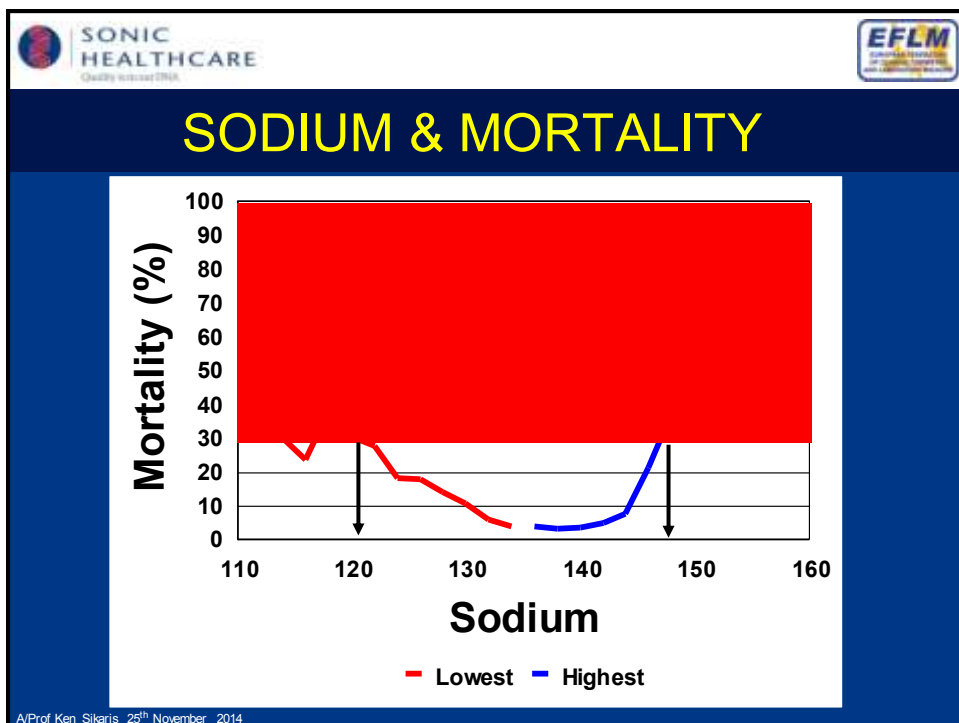
* Worst
** Critical

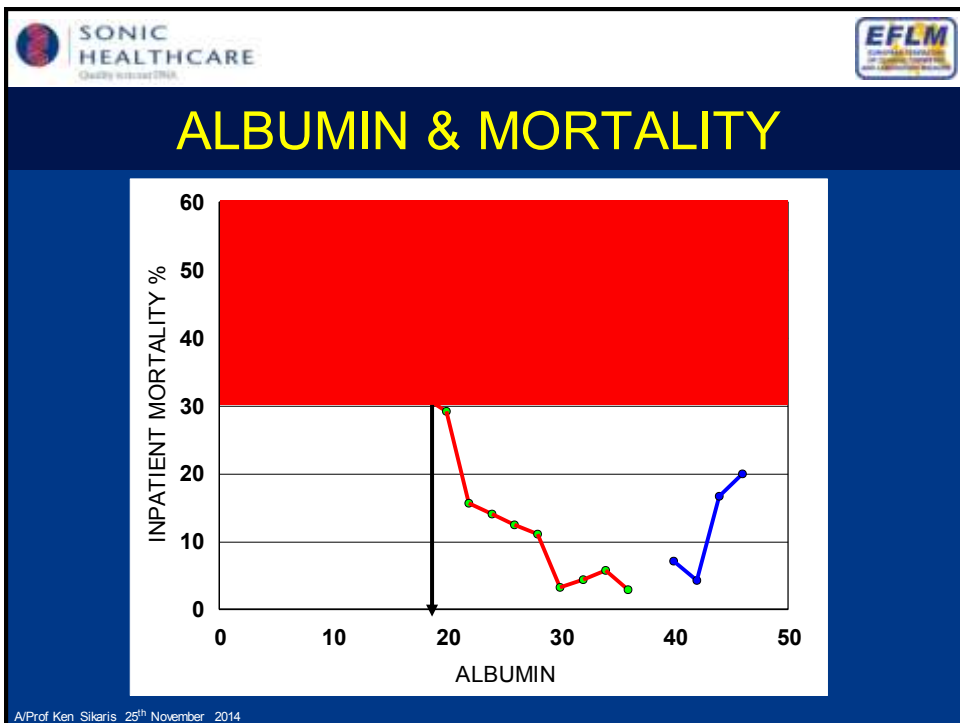
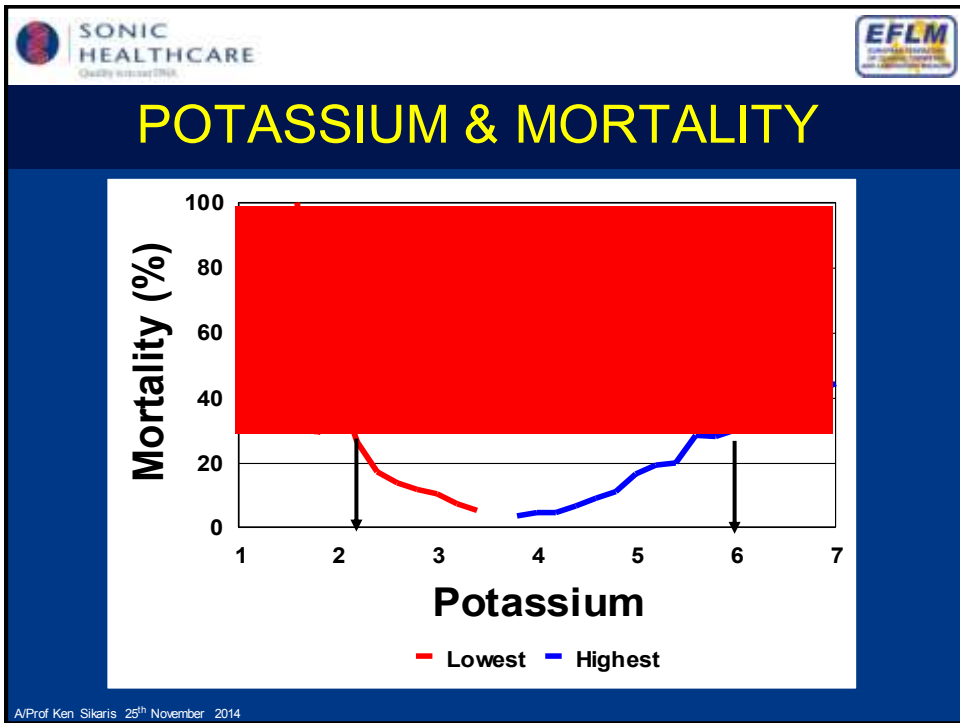
* Mortality range is determined by a doubling of mortality over the baseline level.
** Critical range is determined by a 25% mortality rate associated with that analyte level.

Therapeutic information lies in the range. In chronic disease health status does not affect the results and analysis agree very closely, particularly with respect to most electrolytes. The relationship with plasma bicarbonate may indicate the "protective" effect of metabolic alkalosis in cases of chronic airways disease. With respect to other analytes, for example urate, the mortality ranges are much wider and is unconvincing. This suggests that the clinically "acceptable window" may be more tolerant of hyperuricaemia. Consequently, clinicians interested in preventing mortality would not need to request to observe in its plasma urate level levels even much higher than those indicated by reference intervals. Analyte elevations may, of course, be associated with increasing mortality equally if the analyte measured is the primary effector of the condition (ie, creat). Mortality-based ranges may be of significant benefit in alerting clinicians to life-threatening complications of disease processes.

**1. Clinical Outcome
(a) Outcome**

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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)

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