Performance Criteria for: The Post-analytical Phase

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Chemical Pathologist
Melbourne Pathology, Australia
BSc(Hons), MBBS, FRCPA, FFSc, FAACB, GAICD

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
Sonic Healthcare

10,000 Patients/Day

20,000 Patients/Day
Sonic Healthcare

Europe Pathology $1,144,000

Australian Pathology $1,131,000

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

DEFINING PERFORMANCE GOALS
QUALITY LEVELS: General Concepts

**OPTIMUM STANDARD**
- DESIRABLE
- ACCEPTABLE
- UNACCEPTABLE

**MINIMUM STANDARD**
- UNACCEPTABLE

Model 3: State of the Art

**OPTIMUM STANDARD**
- ACCEPTABLE

**MINIMUM STANDARD**
- UNACCEPTABLE

Best Labs
Most Labs
Worst Labs
Model 2 Biological Variation

- **Optimum Standard**: 0.25 CV,
- **Desirable**: 0.5 CV,
- **Minimum Standard**: 0.75 CV,
- **Unacceptable**

Model 1: Clinical Outcome

- **Optimum Standard**: Health, Wellness,
- **Desirable**: Unwell,
- **Undesirable**: Mortality

A/Prof Ken Sikaris 25th November 2014
DEFINING
THE POST-ANALYTICAL
PHASE

“The Brain to Brain Loop”

Hunger

Collection
Of
Ingredients

Cooking

Meal
Creation

Consumption

EATING

NEED

A/Prof Ken Sikaris 25th November 2014
“The Brain to Brain Loop”

Test Selection

Sample Collection & Transport

Preamanalytical

Analysis / Test Results

Postanalytical

Report Creation

Report Interpretation

CLINICAL NEED

CLINICAL ACTION

ISO 17043

Performance Goals:

Defining laboratory proficiency

General Requirements For Proficiency Testing
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.

Target HbA1c = 7.9%

(Adequate, Good, Adequate, Suboptimal, Poor, No Interpretation)
Report Comments: Education/EQA

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 75g glucose tolerance test is indicated.

Rationale and References
Recommendations of the Australian Diabtes 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 n +8.0 at 1 hour after a 75g load is a positive one 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.

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.
QUALITY LEVELS: Categorical

OPTIMUM STANDARD

Excellent

Good

Acceptable

Minimum Standard

Good

UNACCEPTABLE

Bad

UNACCEPTABLE

MINIMUM STANDARD

Excellent

UNACCEPTABLE

TFT's

Other Hormones

OGTT
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 mIU, following introduction of a laboratory interpretive service.


Quality Assessment of Interpretative Commenting in Clinical Chemistry

Ee Mun Lim,1 Ken A. Sikaris,2,3 Janice Gill,2 John Calleja,2 Peter E. Hickman,4 John Beilby,5,6 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.

<table>
<thead>
<tr>
<th>Case</th>
<th>Official Preferred</th>
<th>Unofficial Preferred</th>
<th>Official Less relevant</th>
<th>Unofficial Less relevant</th>
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<td>Total</td>
<td>748</td>
<td>623</td>
<td>606</td>
<td>615</td>
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</table>
Quality Assessment of Interpretable Commenting in Clinical Chemistry

EE MUN LIM,1 KEN A. SIKARIS,2,3 JANICE GILL,3 JOHN CALLEJA,3 PETER E. HICKMAN,4 JOHN BRIOLY,1,5 and SAMUEL D. VASKARAN5,6

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.

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

SAMUEL D. VASKARAN1,2,*, LESLIE C. LAI2, 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.
**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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**Interpretative Commenting**

Samuel Vasikaran

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

- **DATA**
- **INFORMATION**
- **KNOWLEDGE**
45 y/o man, PSA = 3.2 ug/L

<table>
<thead>
<tr>
<th>D/E</th>
<th>Mean score</th>
<th>Participants' comments</th>
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<tr>
<td>S</td>
<td>0</td>
<td>The PSA value is in normal range. It shows that the 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.</td>
</tr>
<tr>
<td>S</td>
<td>3.5</td>
<td>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 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).</td>
</tr>
</tbody>
</table>

Comment drafted by the Program Committee

Data to Knowledge and Action:

Pathology: Data Rich, Information Poor?
Figure 2. Spectrum of knowledge types
(Adapted from McCormick, "Conceptual and Procedural Knowledge", 1997)
HIERARCHICAL APPROACH TO POST-ANALYTICAL PERFORMANCE CRITERIA

Why reference limits? Why flags?

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<th>S</th>
<th>M</th>
<th>Dob: 16/03/79</th>
<th>Sex: P32</th>
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<td>1600, 16/11/07</td>
<td>Doc: 0</td>
<td>Note: UR: 1125/6427</td>
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<td>Time</td>
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<td>Lab Id.</td>
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</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Units</th>
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<tr>
<td>SODIUM</td>
<td>136</td>
<td>mmol/L</td>
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<tr>
<td>POTASSIUM</td>
<td>4.5</td>
<td>mmol/L</td>
</tr>
<tr>
<td>CHLORIDE</td>
<td>99</td>
<td>mmol/L</td>
</tr>
<tr>
<td>BICARB</td>
<td>28</td>
<td>mmol/L</td>
</tr>
<tr>
<td>UREA</td>
<td>3.6</td>
<td>mmol/L</td>
</tr>
<tr>
<td>CREAT</td>
<td>57</td>
<td>umol/L</td>
</tr>
<tr>
<td>eGFR &gt;90</td>
<td></td>
<td></td>
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<tr>
<td>ANION GAP</td>
<td>14</td>
<td>mmol/L</td>
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<tr>
<td>T-BILI</td>
<td>8</td>
<td>umol/L</td>
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<tr>
<td>ALP</td>
<td>204</td>
<td>U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>33</td>
<td>U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>78</td>
<td>U/L</td>
</tr>
</tbody>
</table>
Unaffected

Affected

Measurand

Level

SENSITIVITY

OPTIMALITY

SPECIFICITY

Outcome Risk

Frequency

23rd November 2014

AC Milan 1

Inter Milan 1

Crowd 75,000
25th April 1999

Essendon 15.18.108
Collingwood 15.10.100
Crowd 73,118

Stockholm.
STRATEGIES TO SET GLOBAL QUALITY SPECIFICATIONS IN LABORATORY MEDICINE

WORLD HEALTH ORGANIZATION

International Union of Pure and Applied Chemistry

International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum, Karolinska Institutet
Stockholm April 24-26, 1999

A/Prof Ken Sikaris, 25th November, 2014
Where we use performance criteria

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

• Reference Intervals
• Clinical Decision Limits
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

Stockholm Hierarchy for Analytical Quality

Table 1. The Stockholm Hierarchy for analytical quality goals. Adapted from Kenny D, et al.16

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.
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**

Hierarchy for Reference Intervals & Decision Limits

<table>
<thead>
<tr>
<th>Table 2. The Stockholm Hierarchy applied to reference intervals and clinical decision limits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical decision limit based on clinical outcome study e.g. HbA1c cut-off based on the presence of diabetes outcome (retinopathy).</td>
</tr>
<tr>
<td>2. Other methods of determining reference interval or clinical decision limit</td>
</tr>
<tr>
<td>a. Reference intervals derived from apparently healthy populations e.g. NORIP, CALIPER.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>3. Published professional recommendations</td>
</tr>
<tr>
<td>a. National or international expert bodies e.g. national urine protein cut-offs.</td>
</tr>
<tr>
<td>b. Expert local groups or individuals e.g. ARQAG, SONIC.</td>
</tr>
<tr>
<td>4. Reference limits set by</td>
</tr>
<tr>
<td>a. Regulatory bodies e.g. prostate-specific antigen (PSA) cut-offs.</td>
</tr>
<tr>
<td>b. Formal Reference Interval Survey e.g. UK Harmony Survey.</td>
</tr>
<tr>
<td>5. Reference limits based on the current state of the art</td>
</tr>
<tr>
<td>a. Published intervals used in postanalytical external quality assurance e.g. pathology interpretation exercises.</td>
</tr>
<tr>
<td>b. Current publications on methodology e.g. textbooks or kit inserts.</td>
</tr>
</tbody>
</table>
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.

Proposed Hierarchy

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

a. investigating the impact of analytical performance of the test on clinical outcomes
b. investigating the impact of analytical performance of the test on the probability of clinical outcomes
c. investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)

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)
Kit Inserts

<table>
<thead>
<tr>
<th></th>
<th>U/L</th>
<th>µkat/L</th>
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<tbody>
<tr>
<td>Men</td>
<td>up to 41</td>
<td>up to 0.68</td>
</tr>
<tr>
<td>Women</td>
<td>up to 31</td>
<td>up to 0.52</td>
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</table>


Textbooks
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.

RCPAQAP Survey 2013: Potassium

Vitros Labs

Low

High
Reference intervals vary much more than results!

BEYOND ANALYTICAL QUALITY:
THE IMPORTANCE OF POSTANALYTICAL QUALITY IN ASSURING CLINICAL VALUE
George S. Cembrowski, MD, PhD

<table>
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<tr>
<th>Tests</th>
<th>Highest CV%</th>
<th>Test</th>
<th>Lowest CV%</th>
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<tr>
<td>Cholesterol (total)</td>
<td>276.6</td>
<td>Cortisol (A1c values)</td>
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<tr>
<td>Prolactin</td>
<td>220.6</td>
<td>Fibrinogen</td>
<td>10.2</td>
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<tr>
<td>Folate</td>
<td>176.8</td>
<td>Valproate</td>
<td>9.3</td>
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<tr>
<td>Lipase</td>
<td>96.7</td>
<td>Iron</td>
<td>9.2</td>
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<tr>
<td>Bilirubin (conjugated)</td>
<td>86.3</td>
<td>Platelet count</td>
<td>8.7</td>
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<tr>
<td>Thyroid Stimulating Hormone</td>
<td>73.7</td>
<td>HB A1c</td>
<td>8.6</td>
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<td>Lactate Dehydrogenase</td>
<td>46.2</td>
<td>Theophylline</td>
<td>7.2</td>
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<tr>
<td>LH (follicular phase)</td>
<td>43.8</td>
<td>Phenobarbitalone</td>
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<td>FSH (follicular phase)</td>
<td>37.4</td>
<td>PSA</td>
<td>6.3</td>
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<td>Amylase</td>
<td>35.3</td>
<td>Bicarbonate (total CO₂)</td>
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<td>WBC count</td>
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<td>Phosphate</td>
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<td>Creatine Kinase (total)</td>
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<td>Albumin</td>
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<td>Hemoglobin</td>
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<td>Alanine aminotransferase</td>
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<td>Hematocrit</td>
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<td>Osmolality</td>
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<td>Alkaline Phosphatase</td>
<td>17.4</td>
<td>Sodium</td>
<td>0.9</td>
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3.3

5.6
4.5
3.9
3.3

Laboratory number

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

Pathology Harmony; a pragmatic and scientific approach to unfounded variation in the clinical laboratory
Jonathan Berg and Vanessa Lane

<table>
<thead>
<tr>
<th>Test name</th>
<th>Units</th>
<th>Range low</th>
<th>Range high</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>3.5</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

Potassium ranges for 45 laboratories in central England

Table 1 Examples of agreed Pathology Harmony clinical biochemistry reference intervals for adults
Model 2: Biological Variability

- a. Investigating the impact of analytical performance of the test on clinical outcomes.
- b. Investigating the impact of analytical performance of the test on the probability of clinical outcomes.
- c. Investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes).

Inherent biological variation and reference values

Callum G. Fraser*

Biological Variability & Reference Intervals

Measurement Uncertainty

Intra-individual Variability

Inter-individual Variability

Reference Interval includes \[ \left[ (CV_A)^2 + (CV_I)^2 + (CV_G)^2 \right]^{0.5} \]
Analytical quality specifications for common reference intervals

Carmen Ricos, Maria Vicenta Doménech and Carmen Perich


Maximum imprecision (with no bias) of \( CV_A \)

\[ < 0.58 \left( CV_I^2 + CV_G^2 \right)^{1/2} \]

Maximum bias (with no imprecision) of \( SE_A \)

\[ < 0.25 \left( CV_I^2 + CV_G^2 \right)^{1/2} \]

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.


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

Model 1: Clinical Outcome

a. investigating the impact of analytical performance of the test on clinical outcomes

b. investigating the impact of analytical performance of the test on the probability of clinical outcomes

c. investigating the impact of the analytical performance of the test on medical decisions (and thereby on the probability of patient outcomes)
Retinopathy – Pima Indians

Diabetes Care 1997;20:1183–1197

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 Angela M. Conin, research biostatistician,1 Thomas Björk, senior consultant,1 Jonas Manjer, associate professor,2 Peter M. Nilsson, professor,2 Anders Dahlén, data manager,1 Anders Bjartell, professor,2 Peter T. Scardino, department chief,1 David Ullert, research fellow/resident,1 Hans Lilja, attending research clinical chemist/professor (adjunct)3

Deaths per 1000

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
Model 1c: Clinician Survey / Expert Opinion

a. investigating the impact of analytical performance of the test on clinical outcomes

b. investigating the impact of analytical performance of the test on the probability of clinical outcomes

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

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®, Constantine N. Aroney, MD, FRACP®, Philip E. Aylward, FRACP, FCANZ, FRCP, FACC®, Anne-Maree Kelly, M Clin Ed, FACEM, FCCP®, Harvey D. White, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZ®, Philip A. Tideman, FRACP®, Jill Waddell, MPH®, Leva Azadi, MPH®, Alison J. Wilson, MBA® and Leah-Anne M. Ruta, PhD®

Table 1. Summary of Recommendations.

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

Reference intervals and units – in adults, non-pregnant

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

Evidence
- Bias Study
- Aussie Normals Study
- Sonic Healthcare Reference Interval Study

Stakeholder Workshops
- Consultation
- Verification
- Implementation

Spreadsheet validation tool
- Flagging Rates
- Harmonised Reference Intervals

A/Prof Ken Sikaris, 25th November, 2014
Australasian Harmonised Reference Intervals

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

Primary role of reference intervals

- **Initially use reference interval**
  - We don’t know what this patient’s result should be
  - Compare this first result to similar people
- **Subsequently use previous result as baseline**
  - What is a significant change?
Inherent biological variation and reference values

Callum G. Fraser*


Significant Change: Biological

Post-analytical: Significant Change

• Clinical Outcome
• Biological Variation
• State of the Art
### Significant Change: Biological Variability

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CV$_A$</th>
<th>CV$_I$</th>
<th>RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.8%</td>
<td>3.1%</td>
<td>8.6%</td>
</tr>
<tr>
<td>ALP</td>
<td>1.4%</td>
<td>6.4%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.0%</td>
<td>25.6%</td>
<td>70.9%</td>
</tr>
<tr>
<td>ALT</td>
<td>0.9%</td>
<td>24.3%</td>
<td>67.3%</td>
</tr>
<tr>
<td>AST</td>
<td>1.1%</td>
<td>11.9%</td>
<td>33.2%</td>
</tr>
</tbody>
</table>
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', Constantine N. Aroney, MD, FRACP, Philip E. Aylward, FRACP, FCANZ, FRCP, FACC, Anne-Marie Kelly, M Clin Ed, FACEM, FFCC, Harvey D. White, FRACP, FACC, FESC, FAHA, FHKCC (Hon), FCSANZ', Philip A. Timeman, FRACP, Jill Waddell, MPH', Leva Azadi, MPH', Alison J. Wilson, MBA' and Leah-Anne M. Ruta, PhD'

Table 1. Summary of Recommendations.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations: serum troponin measurement</td>
<td>N/A</td>
</tr>
<tr>
<td>Where available, high sensitivity troponin assays should be used in preference to</td>
<td></td>
</tr>
<tr>
<td>conventional assays.</td>
<td></td>
</tr>
<tr>
<td>When using high sensitivity troponin assay, a test should be interpreted as positive if level is ≥ 99th centile for reference population OR above an initial baseline level.</td>
<td>Consensus</td>
</tr>
<tr>
<td>At 3 hours after presentation (with at least one assay performed &gt;6 hours from symptom onset), a test using a high sensitivity troponin assay should be interpreted as negative if the level is &lt; 99th percentile AND change from baseline is ≤ 30%.</td>
<td>C</td>
</tr>
</tbody>
</table>

Change in Plasma Sodium Associated with Mortality.
Guerin MD, Martin AL, Sikaris KA, Clin Chem 1992;38:317

<table>
<thead>
<tr>
<th>Maximum Change in Plasma Sodium (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-12</td>
</tr>
<tr>
<td>10.4</td>
</tr>
<tr>
<td>12.4</td>
</tr>
<tr>
<td>14.4</td>
</tr>
<tr>
<td>16.4</td>
</tr>
<tr>
<td>18.4</td>
</tr>
</tbody>
</table>

Significant Change: Clinician Survey
Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art
When to panic over an abnormal result.
George D Lundberg, Med Lab Obs 1972;

Survey of laboratory ‘critical limits’.

• 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.

SOURCE OF CRITICAL LIST

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

Critical Values Comparison

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

Table 4. Adult and Pediatric Median Critical Values

<table>
<thead>
<tr>
<th>Analyte</th>
<th>No. of Institutions</th>
<th>50th (Median)</th>
<th>95th</th>
<th>50th (Median)</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mg/dl</td>
<td>164</td>
<td>10.0</td>
<td>10.1</td>
<td>10.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Magnesium, mEq/l</td>
<td>124</td>
<td>1.7</td>
<td>1.8</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Hemoglobin, male patients, g/dl</td>
<td>157</td>
<td>15.0</td>
<td>18.0</td>
<td>20.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Platelet count, x10^9/μl</td>
<td>162</td>
<td>200</td>
<td>230</td>
<td>300</td>
<td>350</td>
</tr>
<tr>
<td>Activated partial prothrombin time, s</td>
<td>17</td>
<td>5</td>
<td>18</td>
<td>154</td>
<td>42</td>
</tr>
</tbody>
</table>

Critical Limit Survey USA
### Table of critical limits

<table>
<thead>
<tr>
<th>Critical Value</th>
<th>Italian Survey</th>
<th>CAP Q-Probes Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium high, mmol/L</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>Calcium low, mmol/L</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemooglobin high, g/L</td>
<td>171</td>
<td>180</td>
</tr>
<tr>
<td>Hemooglobin low, g/L</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

### Critical values policies in Italian institutions: comparison with the US situation

**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.

<table>
<thead>
<tr>
<th>Critical Value</th>
<th>Italian Survey</th>
<th>CAP Q-Probes Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium high, mmol/L</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>Calcium low, mmol/L</td>
<td>1.4</td>
<td>1.5</td>
</tr>
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<td>171</td>
<td>180</td>
</tr>
<tr>
<td>Hemooglobin low, g/L</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

---

**Critical Limit Survey: Italy**
Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art
## Abnormal Glucose Frequency

### 1:1000 Random Glucose > 25.0 mmol/L

<table>
<thead>
<tr>
<th>Glucose mmol/L</th>
<th>SNP Fasting</th>
<th>Fast EDTA</th>
<th>Fast Serum</th>
<th>SNP Random</th>
<th>Random Serum</th>
<th>AM EDTA</th>
<th>PM EDTA</th>
<th>PM Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>7-9.9</td>
<td>1:7</td>
<td>1:11</td>
<td>1:10</td>
<td>1:4</td>
<td>1:7</td>
<td>1:8</td>
<td>1:5</td>
<td></td>
</tr>
<tr>
<td>10-14.9</td>
<td>-</td>
<td>1:38</td>
<td>1:38</td>
<td>1:13</td>
<td>1:19</td>
<td>1:24</td>
<td>1:16</td>
<td></td>
</tr>
<tr>
<td>20-24.9</td>
<td>1:120</td>
<td>1:204</td>
<td>1:197</td>
<td>1:71</td>
<td>1:49</td>
<td>1:78</td>
<td>1:79</td>
<td>1:53</td>
</tr>
<tr>
<td>30-34.9</td>
<td>1:14055</td>
<td>1:22041</td>
<td>1:23849</td>
<td>1:2109</td>
<td>1:1060</td>
<td>1:2376</td>
<td>1:2073</td>
<td>1:470</td>
</tr>
<tr>
<td>&gt;=40</td>
<td>1:57627</td>
<td>1:132244</td>
<td>n/a</td>
<td>1:10142</td>
<td>1:5564</td>
<td>1:10297</td>
<td>1:7047</td>
<td>1:1660</td>
</tr>
</tbody>
</table>

### 1:1000 Fasting Glucose > 20.0 mmol/L

## Post-analytical: Critical Limits

- Clinical Outcome
- Biological Variation
- State of the Art
1. Clinical Outcome
(c) Expert Opinions

1. Clinical Outcome
(c) Clinician Survey

61-79% clinician agreement
Change in Plasma Sodium Associated with Mortality.
Guerin MD, Martin Al, Sikaris KA, Clin Chem 1992;38:317

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. Silke1,2

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

SODIUM & MORTALITY

Mortality (%) vs Sodium

Lowest Highest
Survey of laboratory ‘critical limits’.  

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

Where are performance criteria relevant?

CLINICAL NEED

Test Selection

Sample Collection & Transport

Analysis

Report Interpretation

CLINICAL OUTCOME