St Vincent's Hospital
A facility of St Vincents & Mater Health Sydney

SYDPATH
ST VINCENT'S PATHOLOGY

Performance criteria for EQA schemes – need for harmonization

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Milan November 2014

The Role of External Quality Assurance

- Confirm assay performance
- Identify poor assay performance
  - Confirm correction of poor performance
- Main Issues
  - Accuracy (precision + bias)
  - Precision
  - Bias (Compared to what?)
- Other:
  - Analytical specificity, interferences
  - Reporting: units, reference intervals
  - Interpretation: case comments

EQA

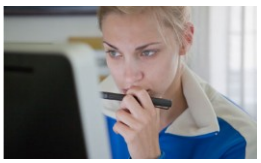
- A place where Quality Standards can be applied
- Assesses the end-product of all other analytical quality activities

Quality Assurance Process

QAP
- Prepare samples
- Distribute samples
- Receive results
- Prepare report
- Send out report

Laboratory
- Receive samples
- Measure samples
- Return results
- Receive report

Interpret report



- Quality confirmed?
- Action if needed

Quality Assurance Process

QAP
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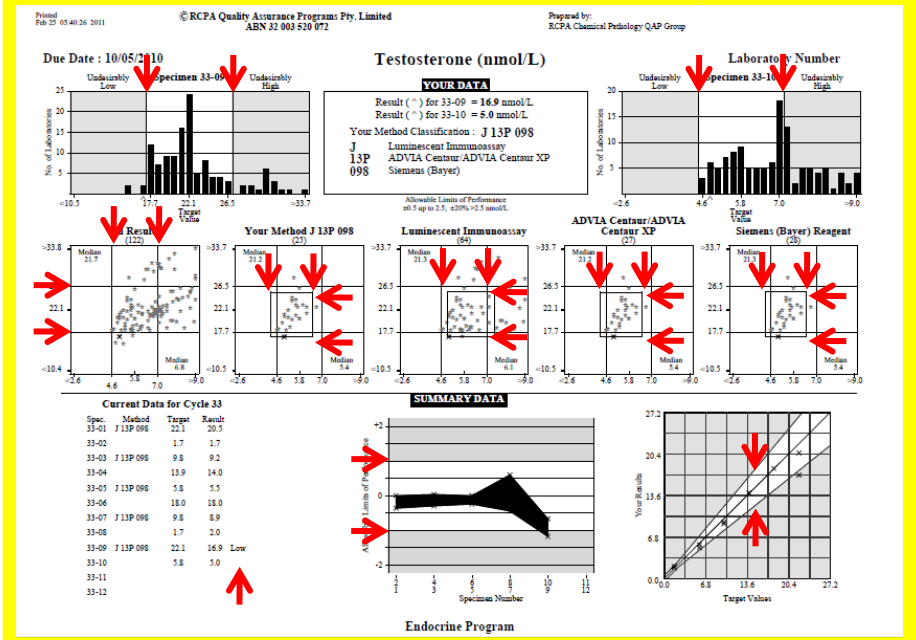
Interpret report
→Quality confirmed?
→Action if needed?

Analytical problems? manufacturers, metrologists, labs, others

Pathology Community: Can we share reference intervals, decision points, monitor a patient across labs

RCPA QAP Interim Report

RCPAQAP
RCPA Quality Assurance Programs



EQA Reports

Interim Report

- After each set of measurements
- Small number of samples (1,2,5)
- May include previous data
- Often analysed as **single results**

End-of-Cycle / Summary Report

- summary of a period
- Larger number of samples
- Statistical analysis (bias, precision) based on **multiple results**

Interpreting **Single** Results

- A **single result** includes effects of both bias and imprecision
- Bias and imprecision effects cannot be separated
- Quality standards assess **"total error"**
- Applies to multiple samples, if they are analysed separately
- Most Interim Reports / some summary reports

Interpreting **Multiple** Results

- From **multiple results: bias** and **imprecision** can be separately identified
- Based in summary statistics
- More results → better information
- Only applies to multiple samples
- Most Summary Reports / some interim reports

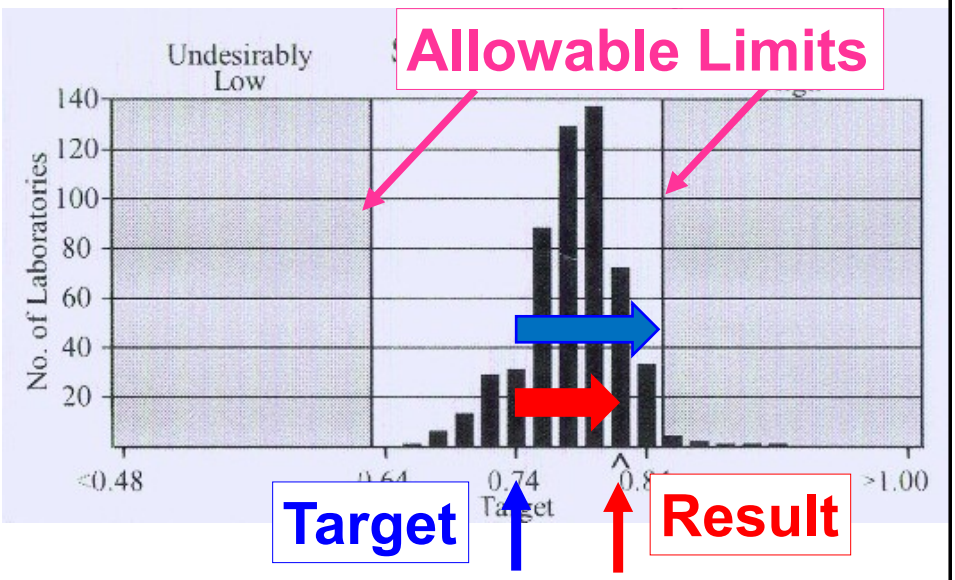
Interpreting **Single** Results

- My focus today is on Quality Standards for interpreting **Single** results
- **Bias** and **imprecision** assessment are vital, but take time to gather quality data
- Bias and imprecision also need quality standards

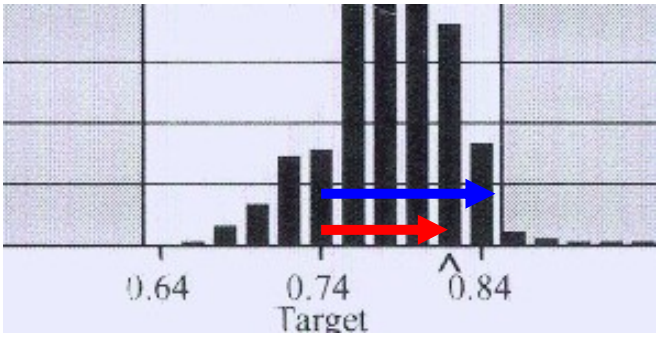
Single Results – the information

- **Result** from laboratory
- **Target** from EQA program
- **Distance** from Target
- Assess Acceptability (**quality standard**)
  - Qualitative
  - Quantitative

Single Result Report (RCPAQAP)



Interpret Report



- "All aspects of pathology are determined by comparison" *(Per Hyltoft Petersen, Sydney, 2005)*
- In this setting: Compare with a Quality Standard

Targets

- These indicate the "correct" result
- Two main types
  - Overall analyte target
    - Reference Method / Material
    - Median
    - Assumes commutability of material in methods
  - Laboratory-specific target
    - Based on method / instrument / reagents etc

Distance from Targets

- Deviation: Lab result value - target value
- Assessment of deviation: compare with a quality standard
- Which quality standard?

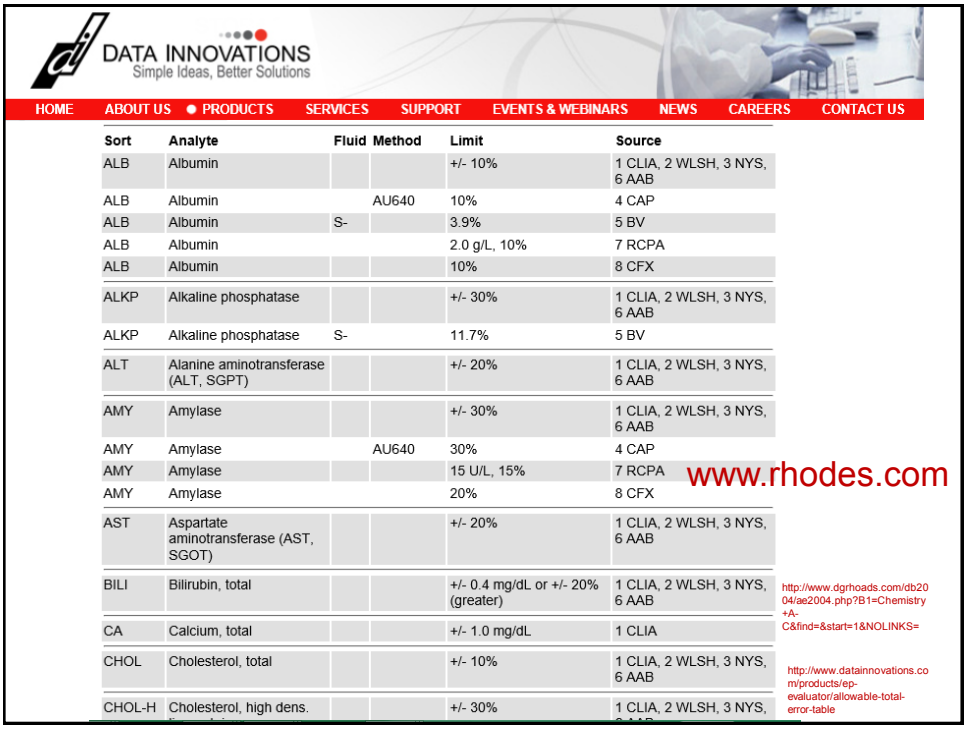
Eur J Clin Chem Clin Biochem 1996; 34:159–165

External Quality Assessment: Currently Used Criteria for Evaluating Performance in European Countries, and Criteria for Future Harmonization

Carmen Ricós[1], *Henk Baadenhuijsen*[2], *Jean-Claude Libeer*[3], *Per Hyltoft Petersen*[4], *Dietmar Stöckl*[5], *Linda Thienpont*[6] and *Callum G. Fraser*[7]

Tab. 3 Currently used European EQA limits (given in % deviation from the target)

	Cholesterol	P_i	Lithium	Lactate dehydrogenase	Urate	Alkaline phosphatase
Denmark	8.1	12.0	–	12.0	13.0	10.0
Netherlands	8.1	–	5.0	3.0	10.0	8.0
Belgium	8.4	14.0	10.0	15.0	15.0	10.0
Germany[a]	18.0	15.0	12.0	21.0	18.0	21.0
Finland	5.0	5.0	5.0	10.0	5.0	10.0
Switzerland	3.0	10.0	6.0	15.0	10.0	15.0
Croatia	10.0	10.0	–	20.0	10.0	20.0
Lithuania	7.0	5.0	–	7.0	7.0	7.0
United Kingdom	7.6	7.8	11.0	13.0	7.7	15.0
Spain	9.8	12.0	22.0	17.0	15.0	22.0
Italy	5.5	9.5	–	10.0	8.0	18.0
France	16.5	–	10.0	20.0	16.0	20.0
Portugal	5.0	8.0	–	16.0	9.0	29.0
RCPAQAP(%)	5.0	10.0	8.0	15.0	7.8	15.0
CLIA (%)	10.0		20.0	20.0	17.0	30.0
Range (%):	**3-18**	**5-14**	**5-22**	**3-21**	**5-18**	**7-30**



Quality Limits - the way forward

- Framework – What are we trying to find out with the limits?
- What Limits?
- In Practice?

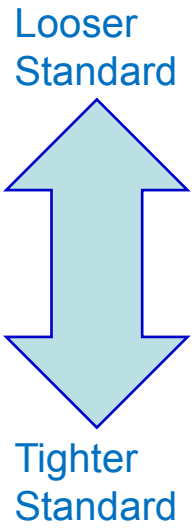
Framework

- What are we trying to find out with the limits?

EQA Quality Standards

What type of standard?

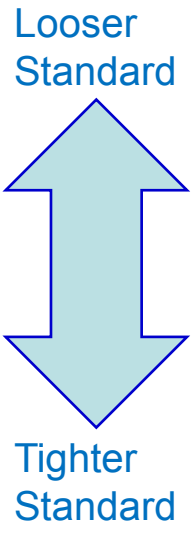
- **Minimum standard**
  - All should pass (except bad labs)
- **Expected standard**
  - Most should pass
  - Aim to improve those which don't
- **Aspirational standard**
  - Some will not pass
  - May need better methods



EQA Quality Standards

Response to failures?

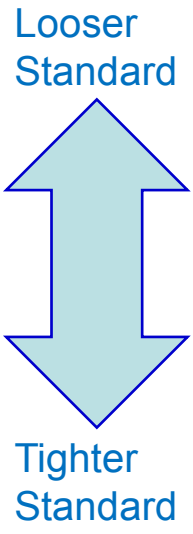
- **Affects registration**
  - USA (CLIA), Germany (RiliBAK)
- **Requires mandatory investigation**
  - Canada?
- **Should be followed up – effort depends on severity**
  - Australia (NATA RCPA)
- **Some failures are expected**



Accuracy Quality Standards

What does it mean to meet the standard?

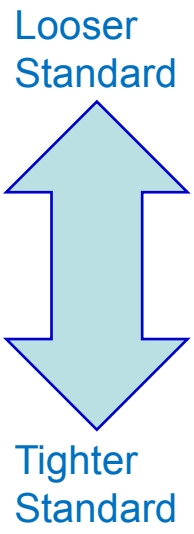
- There may still be benefits from assay improvement
- Most assays are satisfactory
- No further effort is needed on this analyte



Accuracy Quality Standards

What is the clinical effect of (not) meeting the standard?

- Assays need different reference intervals
- The same lab should be used for monitoring a patient
- Assays can share the same reference interval / decision points
- Patients can be monitored across different labs



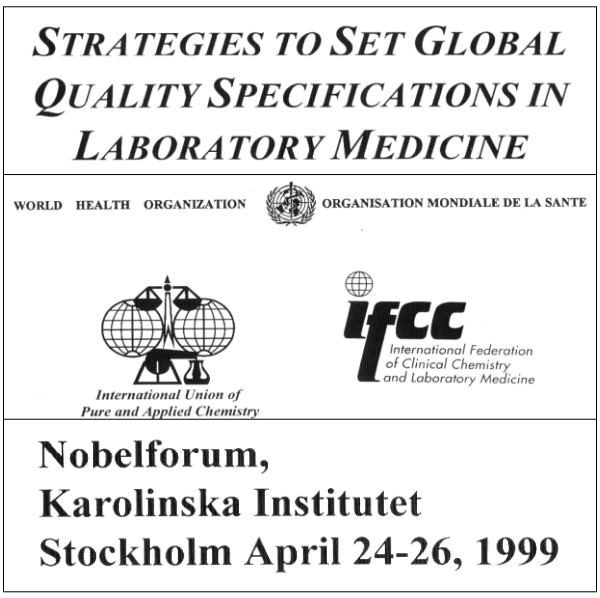
Summary - 1

EQA providers should state the following:

- High-level rationale for setting standards
- Expected response to failures
- Clinical meaning of meeting / not meeting quality standards

What Limits?

- How do we set the limits?



Now exists an internationally agreed hierarchy of preferred methods for establishing performance goals

Stockholm Hierarchy

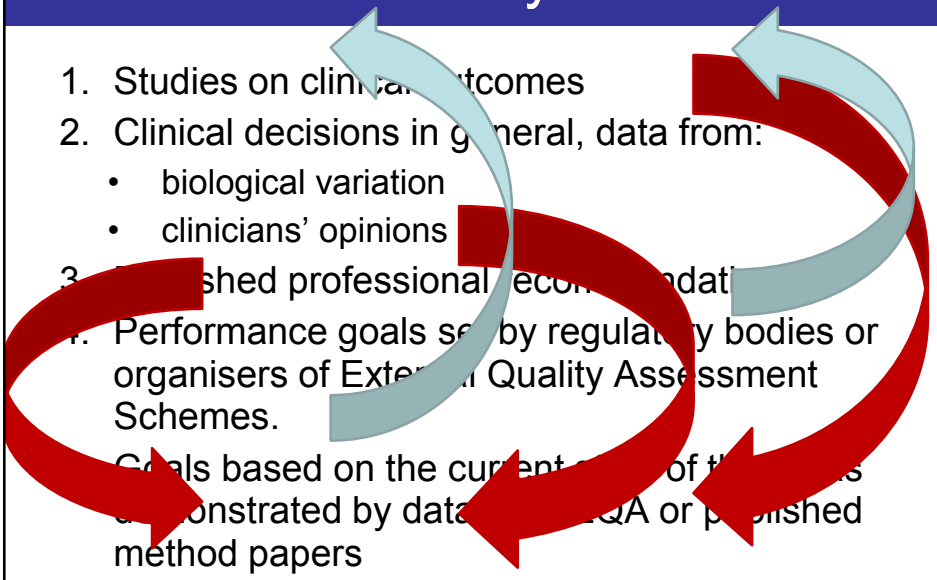
1. Studies on clinical outcomes
2. Clinical decisions in general, data from:
   - biological variation
   - clinicians' opinions
3. Published professional recommendations
4. Performance goals set by regulatory bodies or organisers of External Quality Assessment Schemes.
5. Goals based on the current state of the art as demonstrated by data from EQA or published method papers

An old saying:

- If you have seen one implementation of the Stockholm Hierarchy…

  … you have have seen one implementation of the Stockholm Hierarchy

Stockholm Hierarchy



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Stockholm Revision

- *Model 1 - Based on the effect of analytical performance on clinical outcomes*
- *Model 2 - Based on components of biological variation of the measurand*
- *Model 3 - Based on state of the art*

With thanks to Xavier Albe and CSCQ

How is poor performance defined among EQA organisations?

Xavier Albe
Quality Control Centre Switzerland

Centre Suisse de Contrôle de Qualité
Schweizerisches Zentrum für Qualitätskontrolle
Centro Svizzero di Controllo della Qualità
Quality Control Centre Switzerland

Participants to the survey

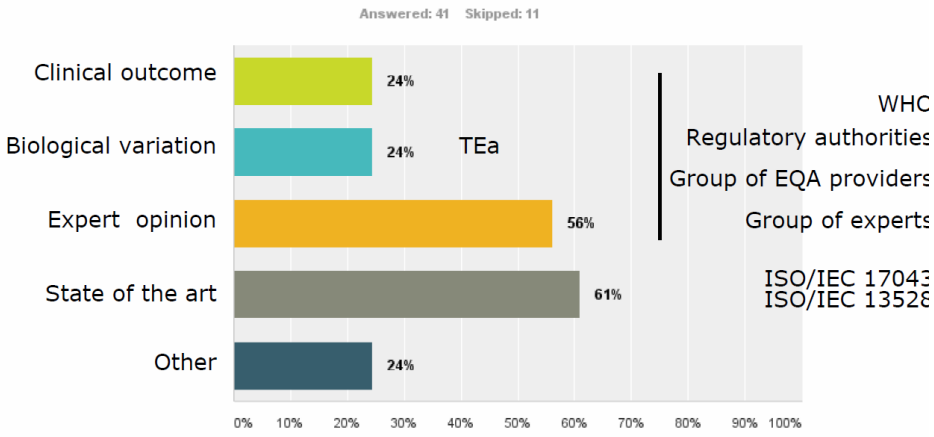
ÖQUASTA, Austria	Hospital Clinic . University of Barcelona, Spain
Institute of Public Health, Belgium	SEQC, Spain
SEKK, Czech Republic	Sociedad Española de Hematología y Hemoterapia, Spain
DEKS, Denmark	CSCQ, Switzerland
Labquality, Finland	Academic Medical Center, The Netherlands
Reference Institute for Bioanalytics, Germany	ECAT Foundation, The Netherlands
Instande e.V., Germany	Erasmus Univ. Medical Center, The Netherlands
CMCEQAS, India	Maastricht Universitu Medical Center,The Netherlands
IEQAS, Ireland	Radboud University Hospital Nijmegen, The Netherlands
Programma Regionale Per La Ricerca Biomedica, Italy	SKML, The Netherlands
Noklus, Norway	Randox, UK
Instituto Nacional de Saude, Dr Ricardo Jorge, Portugal	UK NEQAS General Haematology, UK
RoEQALM, ROMANIA	UK NEQAS for Immunology, Immunochemistry & Allergy, UK
National Centre for External Quality Assessment in Laboratory Medicine, Russia	UK NEQAS for Microbiology, UK
University Medical Centre Ljubljana, Slovenia	

N=29

sorted by country

Centre Suisse de Contrôle de Qualité
Schweizerisches Zentrum für Qualitätskontrolle
Centro Svizzero di Controllo della Qualità
Quality Control Centre Switzerland

2. On what basis is poor performance evaluated?



Multiple Standards

Multiple levels of same type of standard:

- Eg: Analytical performance meets:
  - Optimal
  - Desirable
  - Minimal levels

Different types of standards

- Eg: Statistical and clinically based standards on same report
  - Same result(s) may meet one and fail another (eg SKML The Netherlands)

Applying the Stockholm Criteria

Done by ***People*** in ***Organisations***

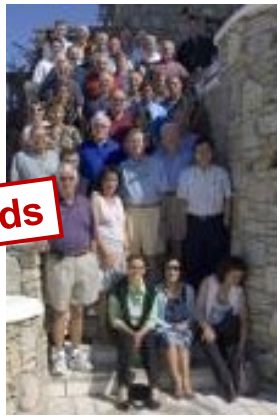
- Using background principles
- Using information
- Common Information (eg Ricos Database)
- Specific information (local EQA data*)

Ref… …val Variation

EQA Quality Standards

- EVEN given the same data, laboratory scientists WILL interpret it differently.
- Add in variability of data reviewed
- Variation in … …vals:
  - Always seen
  - AN EXPECTED OUTCOME!

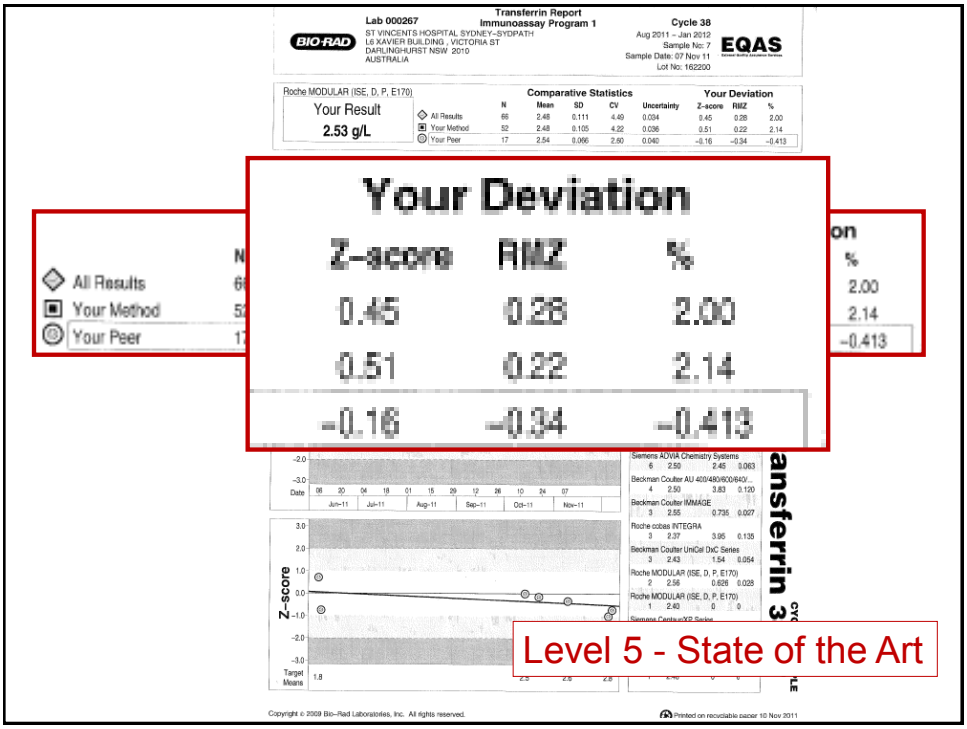
EQA Quality Standards



Level 5 – State of the Art

Statistical analysis (State of the art)

- Commonly Used
- Compare results against other submitted results
- Target: Usually middle of group
- Limits: typically +/- 2 or 3 SD
- Severity assessment: z-score (or similar)



Statistical Analysis

- Compares lab with other similar labs
- Alerts to possible analytical / work practice problem.
- (clinical meaning uncertain)

Statistical Issues - Standardisation

- Outlier exclusion
- Use with other limits
- Limit at 2SD, 3SD or other
- Small method groups
- Identification of method groups

Higher Level Quality Standards (1-4)

- How are they set?

- Using Stockholm Criteria
- Different levels for different analytes
- Using one level of the Stockholm criteria

- (in practice: Biological Variation)

Revision of ALP - RCPAQAP

- Use highest suitable level on the hierarchy
  (in practice – biological variation)
- Do not set unachievable goals
  (state of the art)
- Aim to improve laboratory performance

RCPAQAP
RCPA Quality Assurance Programs

Commentary

'Allowable Limits of Performance' for External Quality Assurance Programs – an Approach to Application of the Stockholm Criteria by the RCPA Quality Assurance Programs

***Graham RD Jones,[1,2] Kenneth Sikaris,[3,4] Janice Gill[5]**
[1] SydPath, StVincent's Hospital, Darlinghurst, NSW, 2010, [2]University of NSW, Randwick, NSW, [3]Melbourne Pathology, Melbourne, Vic. [4]Melbourne University, Melbourne, Vic.[5] RCPA Quality Assurance Programs Pty Ltd, Adelaide, SA, Australia.
*For correspondence: Dr Graham Jones, gjones@stvincents.com.au

Clinical Biochemist Reviews 2012;33:133-9

RCPAQAP
RCPA Quality Assurance Programs

RCPA ALP

We are producing:

- An agreed definition
- An agreed set of criteria
- An agreed process
- Testing of proposed changes

To produce defensible, robust quality standards

RCPAQAP
RCPA Quality Assurance Programs

Revision of ALP

ALP are **applied** to Total Error

Used in interim reports

Single results include bias and imprecision

Will use categories of CV:

1,2,3,4,5,6,8,10,12,15,20,25,30%

Round to nearest category

Change between absolute and percentage based on precision profile

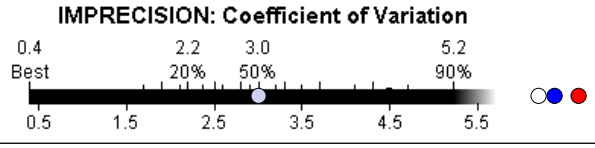
RCPAQAP
RCPA Quality Assurance Programs

Process

- Aim to use tightest limits possible
- Within limitations of State of the art (can be achieved by ~80% of labs)
- Analyte-specific criteria

Ranking of criteria:

- Based on within-subject biological variation
  - Optimal, Desirable, Minimal
- Based on within and between subject BV
  - Optimal, Desirable, Minimal

CRITERIA	**ANALYTE:**		Aspartate Transaminase	
Current ALP	+/- 8 to 60 , 15%		Reporting Interval	1 (22-388)
Reference Interval	10-40 IU/L		Decision Limit	40 IU/L
Discuss:				
Clinical Need	Data	Used both for diagnosis and monitoring.		
	Discus.	No relevance to lower limit		
Biological Variation	Data	CVi = 11.9%, CVg = 17.9%		
	Discus.	Desirable imprecision is 6.0% and optimal imprecision is 3.0%		
Profession Defined	Data	Professional median 15%		
	Discus.			
Current Performance	Data			
	Discus.	Labs can achieve		
Other (eg existing practice or Publications)	Data			
	Discus.			
CONCLUSIONS	ALP:	+/- 5 to 40, 12% (desirable imprecision)		
	Discus.			

Meaning of ALP

Analyte	New ALP					
	±	To	Then %	Comment	Level	Basis
Conj Bili	3	15	20%	Same	Optimal	Imprecision
Calcium	0.10	2.50	4%	Same	Minimal	Imprecision
Chloride	3	100	3%	Same	Minimal	Total Error
Cholesterol	0.3	5	6%	Looser	Desirable	Imprecision
CK-MB	3	15	20%	Looser	Desirable	Imprecision
Creat Kinase	15	125	12%	Tighter	Optimal	Imprecision
Creatinine	8	100	8%	Tighter	Minimal	Imprecision

Basis

"Total Error" – Can share reference interval

"Imprecision" – Can Monitor patient across labs

Level

"Optimal" – no need to improve

"Desirable" – satisfactory

"Minimal" – just satisfactory

RCPAQAP
RCPA Quality Assurance Programs

Definition

- The Allowable Limit of Performance (ALP) is the analytical range around a central value
- It provides a simple tool to allow a rapid, standardised assessment of QAP results in both numerical and graphical report formats.
- A result outside the ALP should alert the laboratory that that their assay may produce results that are at risk of detrimentally affecting clinical decision making.

RCPAQAP
RCPA Quality Assurance Programs

ALP are Not

- An optimal standard for assay performance
  - better care may result from better performance
- A standard which necessarily indicates a danger to patients if it is not met
  - results outside the ALP are not always dangerous
- Limits for use in internal QC protocols.
  - the limits can be (and are) misused

RCPAQAP
RCPA Quality Assurance Programs

Allowable Limits of Performance

(RCPAQAP) ALP are the "reference intervals" of QAP reports

RCPAQAP
RCPA Quality Assurance Programs

Application - Common Reference Intervals

SPECIAL REPORT:

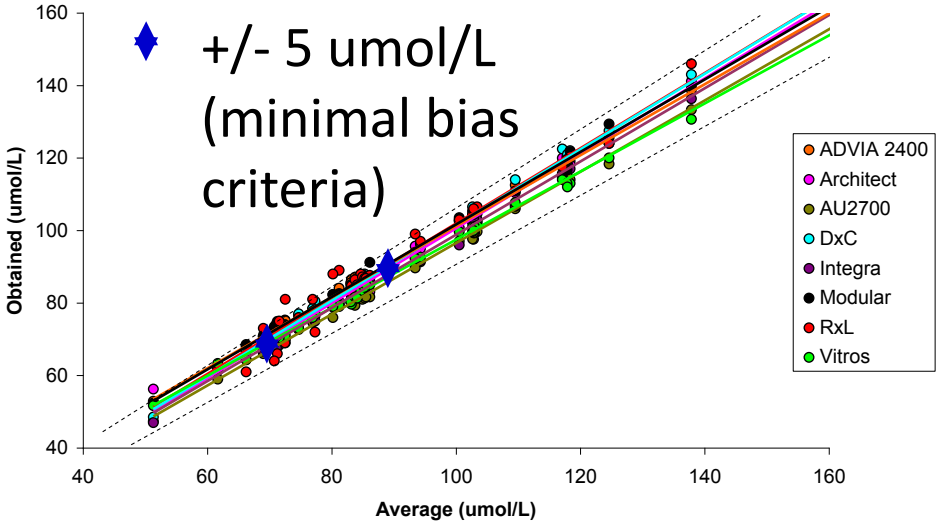
Adult and paediatric common reference intervals in Australia and New Zealand for a first panel of chemistry analytes

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

- AACB, RCPA

towards global harmonisation

Creatinine - Australia
2011 survey, 7 methods, 21 labs



Thanks to Gus Koerbin and AACB Harmonisation Group

able 1 Australasian Harmonised Reference Intervals for Adults (AHRIA) *

Analyte	Male	Female
Sodium	135 – 145 mmol/L	
Potassium **	3.5 – 5.2 mmol/L	
Chloride	95 – 110 mmol/L	
Bicarbonate	22 – 32 mmol/L	
Creatinine ***	60 – 110 µmol/L	45 – 90 µmol/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	0.70 – 1.10 mmol/L	
Lactate Dehydrogenase [L to P] (IFCC) *****	120 – 250 U/L	
Alkaline Phosphatase ******	30 – 110 U/L	
Total Protein	60 – 80 g/L	

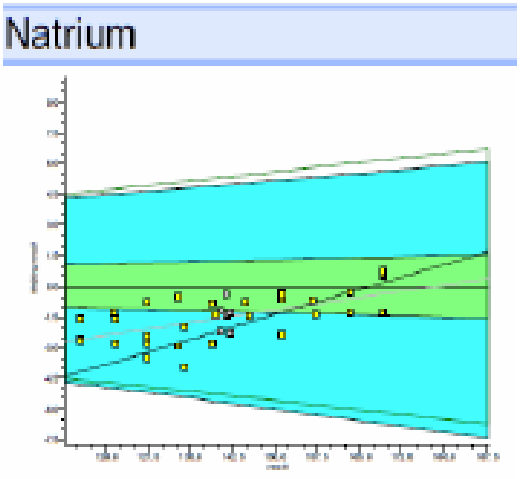
Application

- Using QAP limits for quality planning
- Calculate sigma value and plan QC
- Recently reviewed “QC Update” September 2014 AAAB Adelaide (Thanks to BioRad)
- Some limits too tight for this process

Other Programs

SKML – The Netherlands

- Statistical
- Total Error
- Graphical + scoring
- Concentration dependent



	Concentration	Allowable Bias	Allowable variability	Allowable Total Error
Total Cholesterol	5.0 mmol/L [Desirable[1]]	4.00%	2.70%	8.50%
HDL-Cholesterol	1.0 mmol/L [Desirable[1]]	5.20%	3.60%	11.10%
	1.0 mmol/L [Achievable]	10.00%	3.60%	15.90%
Glucose	7.0 mmol/L [Desirable[1]]	2.20%	2.90%	6.90%
	2.0 mmol/L [Achievable]	+/- 10% absolute		
HbA1c	50 mmol/mol [Desirable[1]]	2.2%*	2.5%*	6.3%*
	50 mmol/mol [Achievab	2.60%	2.50%	7.70%
Creatinine	75 umol/l [Desirable			6
	75 umol/l [Achievab			6

Minimum Analytical Performance Standards (MAPS)

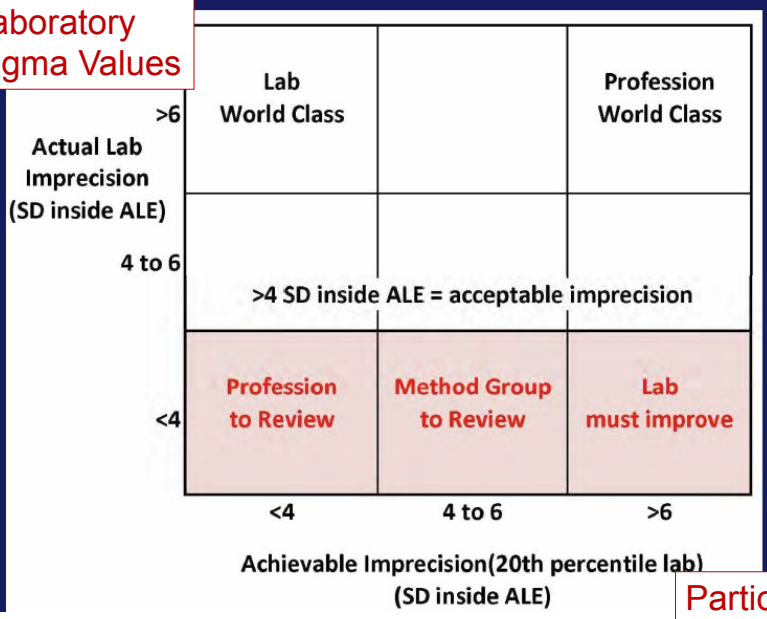
UK - 2010

Pilot

Lab v Industry

3x3 grid – your performance v 20th percentile

Laboratory Sigma Values

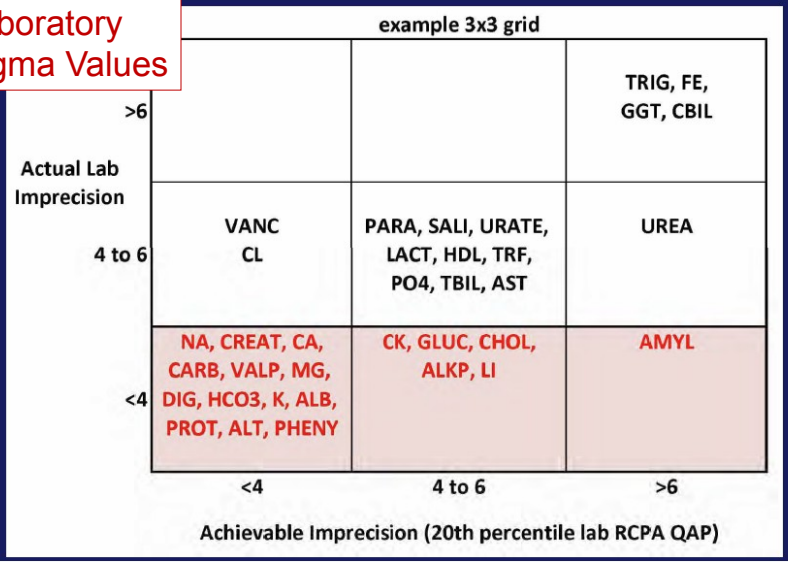


Participant Sigma Values

Mark Mackay AACB QC Satellite meeting 2013

3x3 grid – real lab v 20th percentile – Cycle 92

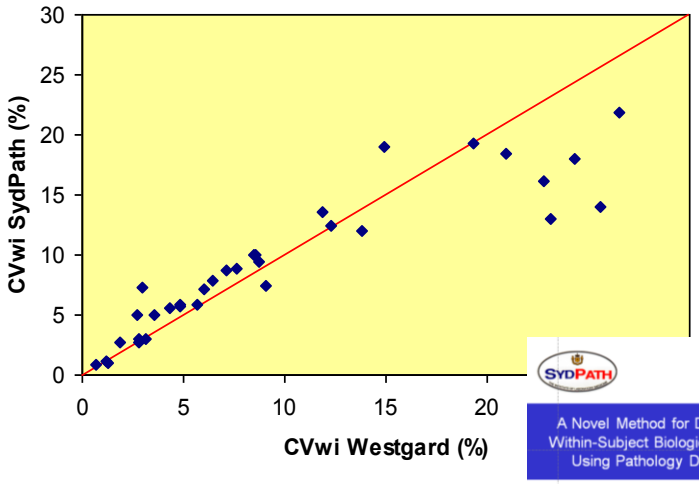
Laboratory Sigma Values



Participant Sigma Values

Mark Mackay AACB QC Satellite meeting 2013

CVi: Data Mining v Ricos Database

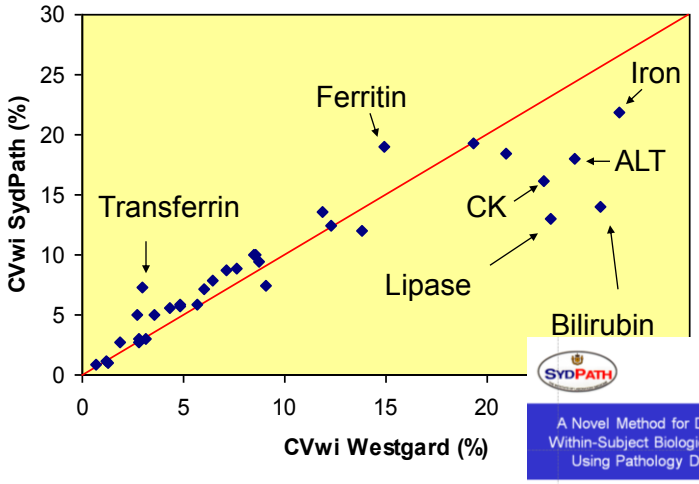


A Novel Method for Determining Within-Subject Biological Variation Using Pathology Databases

Graham Jones
Department of Chemical Pathology
St Vincent's Hospital, Sydney

AACB ASM 2005

CVi: Data Mining v Ricos Database



A Novel Method for Determining Within-Subject Biological Variation Using Pathology Databases

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AACB ASM 2005

Conclusions

- Harmonised EQA Quality Standards?
- No (or at least not yet)
- Will only happen with collaborative effort

Harmonised quality standards

All EQA programs should:

- State the nature of the standards
- State the expected response to standards
- State how they were determined
- State what the effect of compliance means

EQA programs may

- Provide more than one type of standard
- Provide more than one level of standard of the same type

Thank you