Are Commercial Analytical Systems Fulfilling goals based on Medical Relevance?

A/Prof Graham Jones

Department of Chemical Pathology

St Vincent's Hospital, Sydney

Are we good enough?

If not, what will we do about it?

Thanks to Dr Ken Sikaris (Melbourne Pathology), Jan Gill (RCPA QAP)

Summary

- Background Concepts
- QC
- EQA

My comments will be added in this type of text

Roles

Profession (e.g., IFCC, JCTLM): Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

⬇

Diagnostic manufacturers: Implement suitable analytical systems (platform, reagents, calibrators, controls) fulfilling the above established goals

⬇

End users (clinical laboratories): Survey assay and laboratory performance through
- IQC: testing system controls to confirm and verify manufacturer's declared performance of commercial systems (CE marked – virtually unbiased)
- EQA (true value in commutable materials): defining uncertainty of laboratory measurements

(National) Laboratory Collaboration

Medical decision making

- Pathology results are (only) used to assist with medical decisions
- Errors may lead to a patient being:
  - wrongly given treatment
  - wrongly denied treatment
  - wrongly investigated further
  - wrongly not-investigated further

Medical errors

- An error in one result – may affect one patient
- An error in an assay (eg bias) – may affect many patients
- An error in a reference interval – may affect many patients

Medical decision making

- Pathology results are (only) used to assist with medical decisions
- Errors may lead to harm being:
  - wrongly giving treatment
  - wrongly denied treatment
  - wrongly investigated further
  - wrongly not-investigated further

Many Patients

Effect on medical decision-making defines our quality standards

Waste

- Unnecessary testing costs:
- Germany 1.5 Billion US$ per year
  - German Health Report 1998
- USA 7.5 Billion US$ per year
  - Willie May, Chief Analytical Chemistry NIST
- Australia? (0.5 Billion A$)

Analytical quality is important: to patients (and payers)

Murphy KE et al. J. Anal. At. Spectrom., 2002, 17, 469–477

Factors Affecting Blood Tests

- Patient

- Collection

- Measuring

- Reporting

3rd September 2010

Interpretation of Pathology Results

All results interpreted by comparison:

- **with a population reference interval**
  - **Method used to set interval**
- **with a medical decision point**
  - **Method(s) used in clinical trial(s)**
- **with a previous result from the same patient (monitoring)**
  - **Same method at a previous time**

Professor Per-Hyltoft Petersen – Sydney 2005

Interpreting Pathology

- EVERY result interpretation is affected by uncertainty in TWO items.
- A result on its own is meaningless!
- **Laboratories need to put as much effort into the comparator as into the result.**
- **Comparator: literature, other labs outside direct laboratory control**

Stockholm Hierarchy

Strategies to Set Global Quality Specifications in Laboratory Medicine

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

International Union of Pure and Applied Chemistry

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum,
Karolinska Institutet
Stockholm April 24-26, 1999

Stockholm Consensus Conference on Quality Specifications in Laboratory Medicine

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 from current

Stockholm Criteria

- Used within my lab for:
  - Assessment of method validations
  - Assessment of long term QC results
  - Assessment of EQA results

- Use highest level possible

Stockholm hierarchy vital for quality assessment within laboratories

ISO 15189

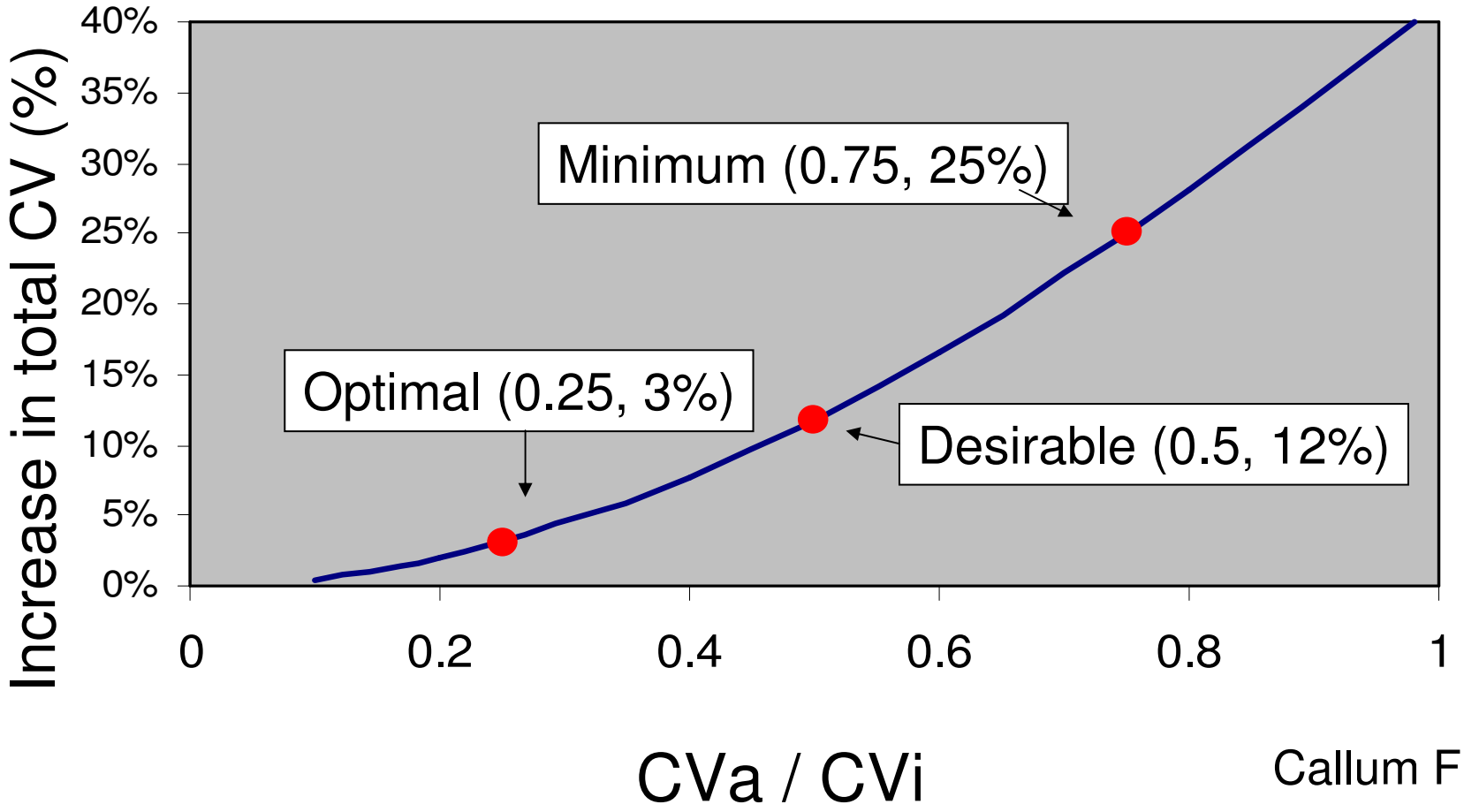
- ***3.8 Clinical Laboratory***
  - examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention and treatment of disease
- ***5.5.1 Examination Procedures***
  - *The laboratory shall use examination procedures…which meet the needs of the users of laboratory services and are appropriate for the examinations.*

Diagnosis vs Monitoring

- **Diagnosis**
  - Compare to Others
    - Healthy / Diseased
    - Reference Intervals ($CV_i + CV_g$)
    - Imprecision and bias
- **Monitoring**
  - Compare to Self
    - Worse / Better / No change
    - CV_i
    - Imprecision (bias is cancelled)

Harder to achieve

Precision Goals - BVi



Precision goals have <u>meaning</u>:

known (small) effect on total result uncertainty

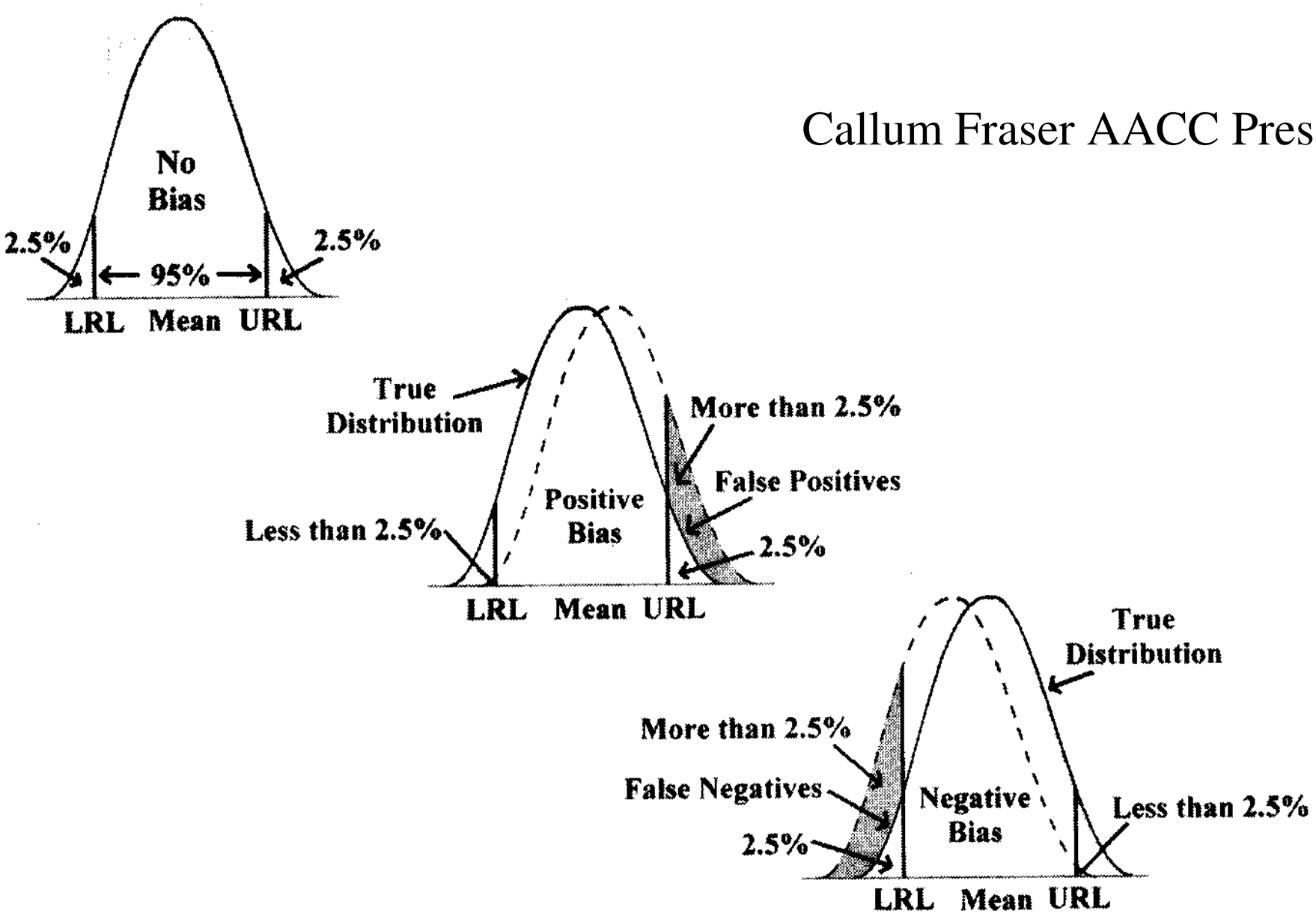
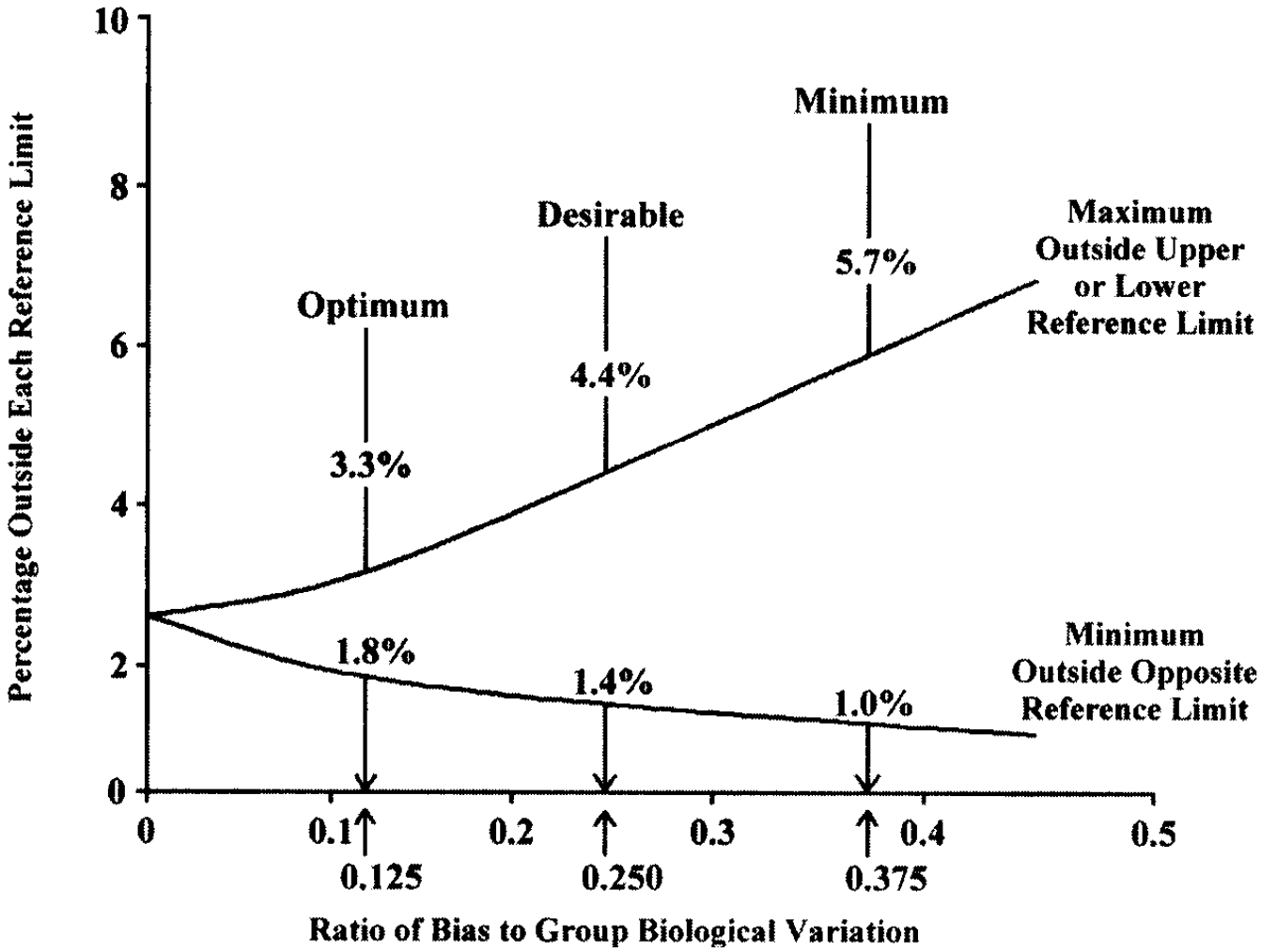


Figure 2.7 Effect of Bias on Reference Values

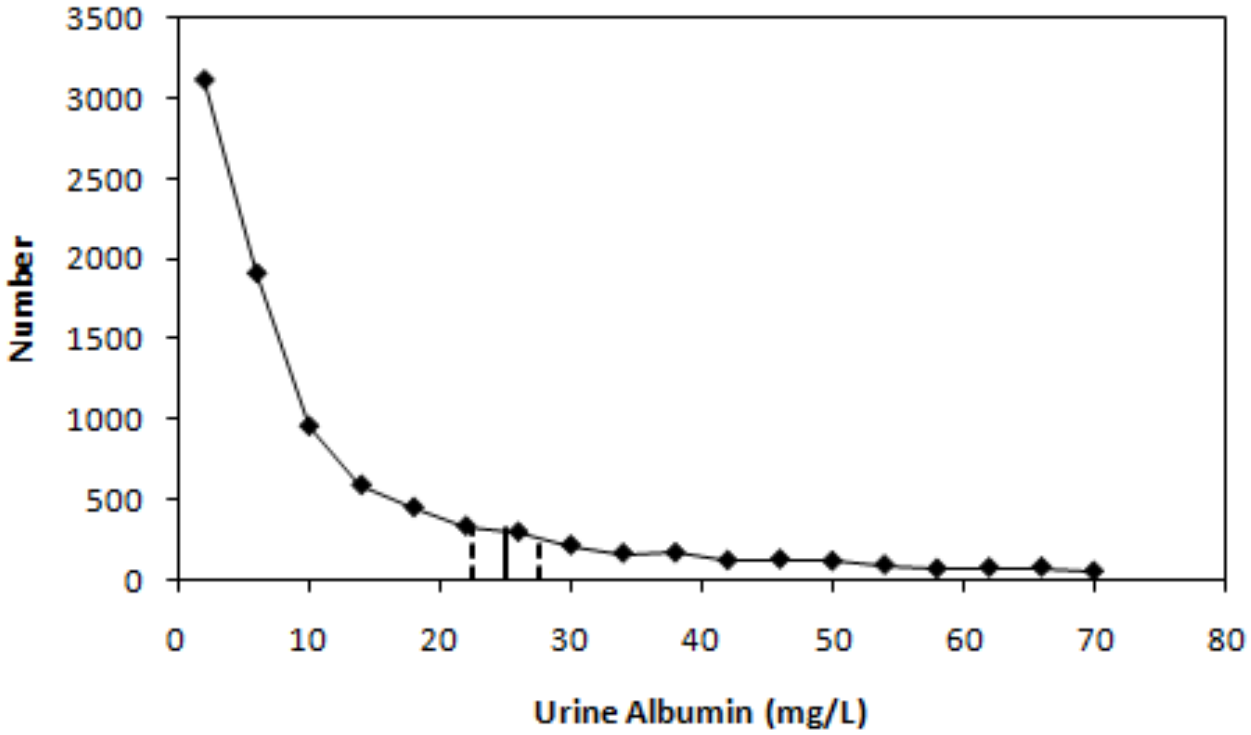


Callum Fraser

Meaning: known (small) change in flagging rate

Bias Criteria

- Distribution of urine albumin concentrations submitted to a routine pathology lab (n=9000 samples, 1 per patient).
- Dashed lines: bias of +/- 10% at 25 mg/L.
- Changes the positivity rate from 9% to 7% or 11%.
- A smaller bias will have a lesser effect.



Importance of QA

- **If there is no comparison between laboratories (ie EQA) – there *will* be differences**

  - G Jones

- Even if there is EQA there may be differences – it is just that we know about them.

Common Databases

- Doctors desktops
- Over 90% of GPs computerised (Aust)
- Now able to **integrate** results from more than one laboratory
  (HL7, atomised results
  LOINC)

- Regional databases
- National databases

Health Technology

- Portable electronic medical records
- Internet
- Smart-Card

- Want to combine results from multiple labs

DISCUSSION PAPER

E-Health: Enabler for Australia's Health Reform

Prepa

27 Nov

1. R ,"

... make the implementation of a fully functional pathology solution available in a very short time-scale..

- **E-Pathology** – The penetration of pathology into clinical practice is all pervasive. Considerable progress has been made which would make the implementation of a fully functional pathology solution available in a very short time-scale initially in specific sites with a view to national adoption. This has been a key project undertaken by NEHTA. This will require review of improved times for result reporting[8] and adherence to principles of Quality use of Pathology.

Obama Wants E-Health Records In Five Years

President-elect says medical information on all Americans should be digitized by 2014.

By K.C. Jones
InformationWeek
January 12, 2009 03:53 PM

President-elect Barack Obama said he wants the federal government to invest in electronic health records so all medical records are digitized within five years.

Obama announced the plans and the deadline during a speech at George Mason University in Fairfax, Va., on Thursday.

"This will cut waste, eliminate red tape, and reduce the need to repeat expensive medical tests," he said, adding that the switch also would save lives by

We NEED to be able to combine results in a database, safely & effectively.

Common Databases

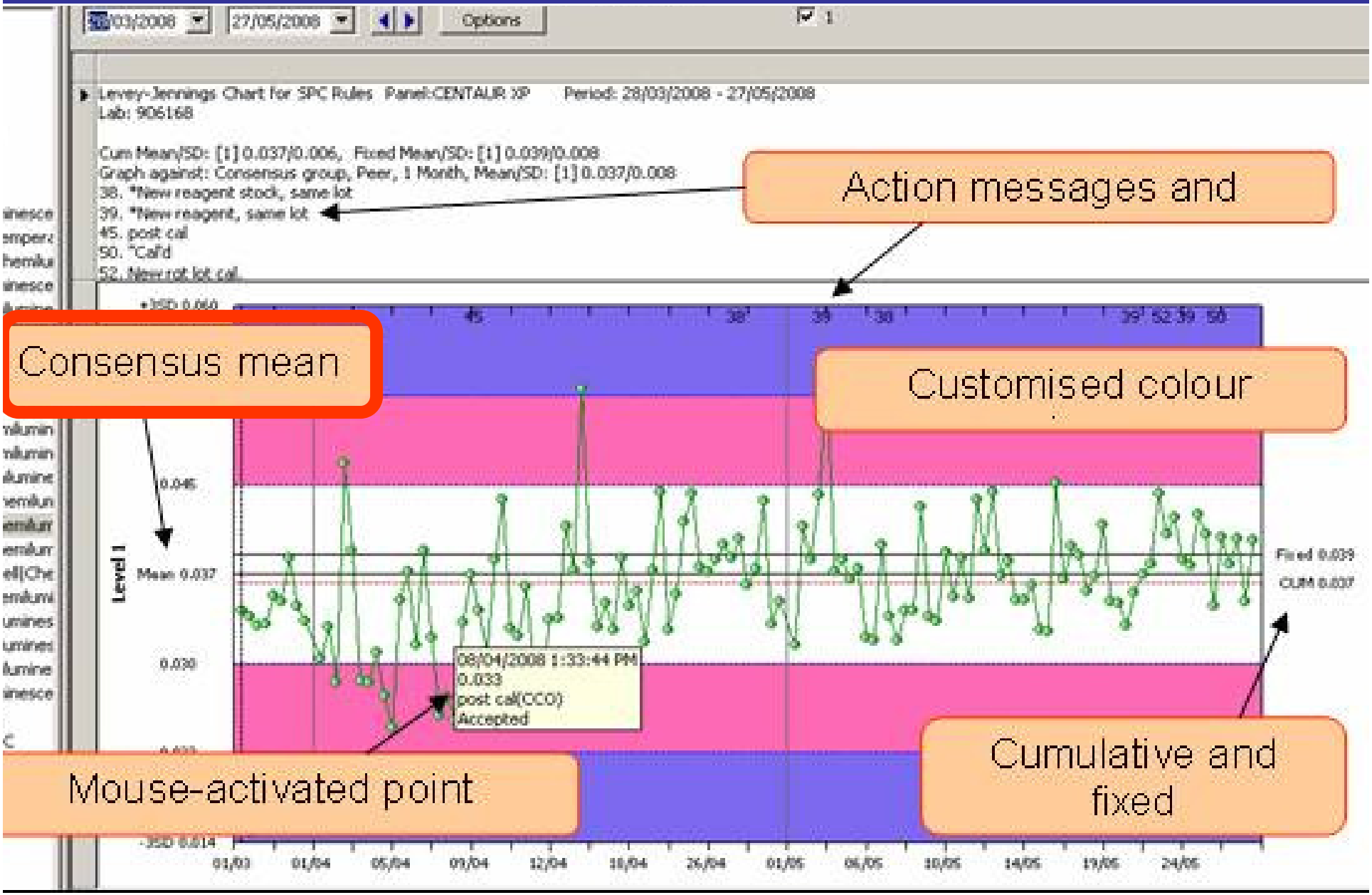
- Combine results from different labs
- Are results close enough to combine?
  - Need Criteria
  - Need Data
  - Need Organisation
  - Need Coding
  - Need ongoing assessment

Responsible entity is a regional, national or other relevant body

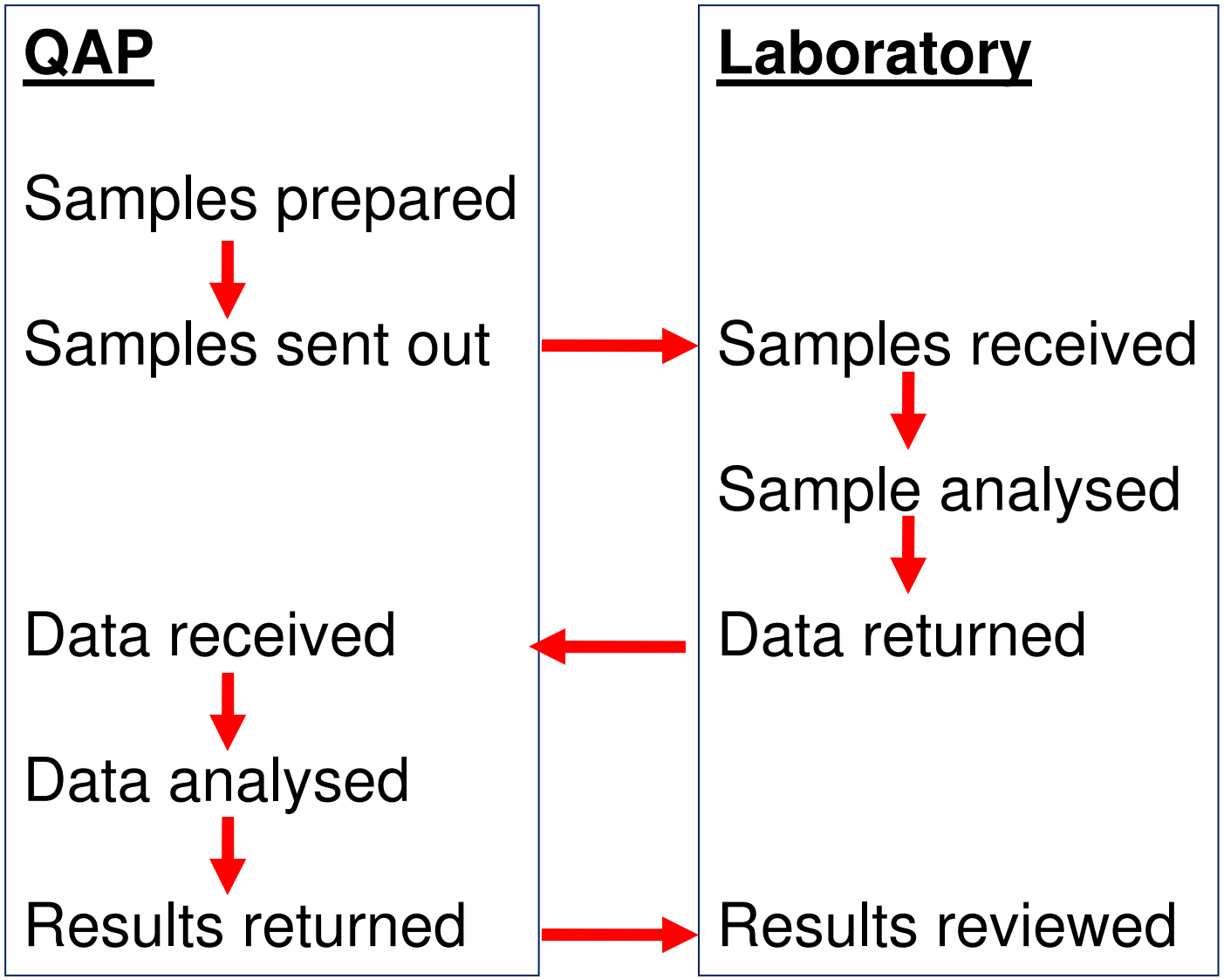
Quality Assurance

- QC – updates
- QA – standard model
- QA – revised model

Bio-Rad Unity RealTime

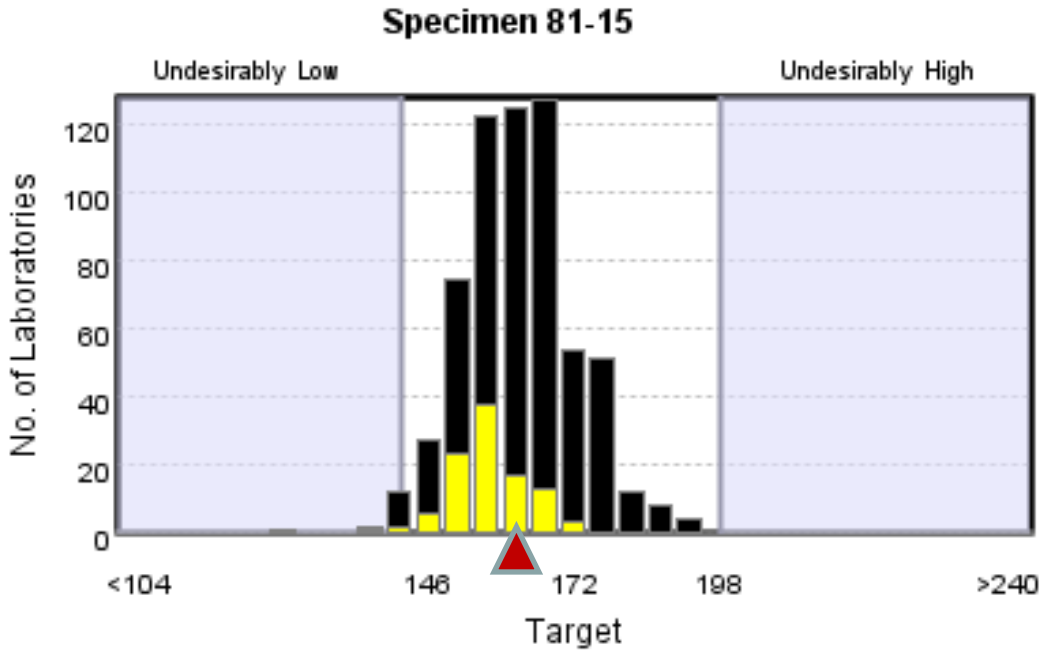


Standard QAP



Traditional QA

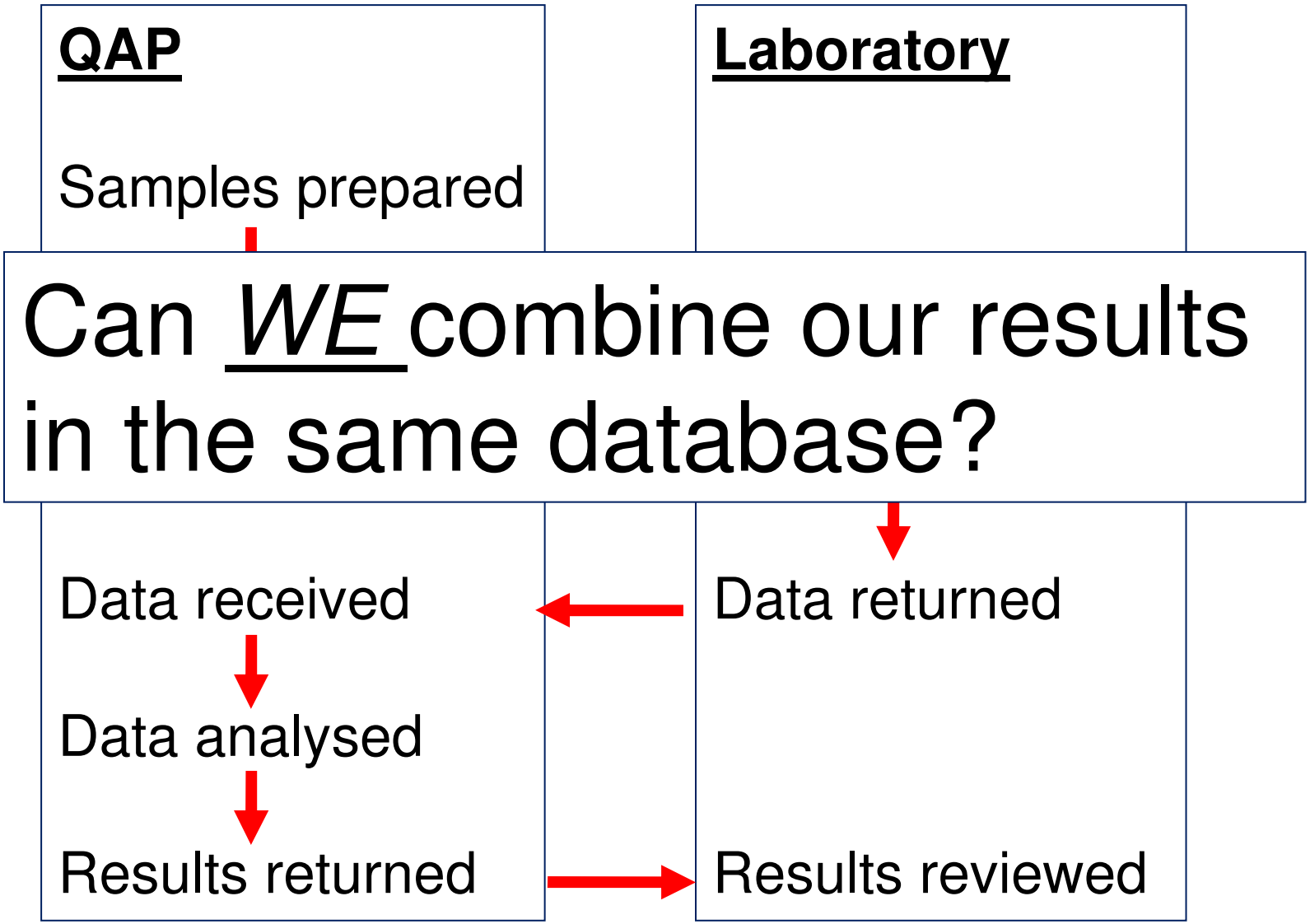
- Is ***My*** lab OK?



- Are my results:
  - Within Program Limits
  - Within method group

  - If not, ***I*** take some action

Revised QAP


QAP
Laboratory
Samples prepared
Can WE combine our results in the same database?
Data received
Data analysed
Results returned
Data returned
Results reviewed

QAP - The New Question

- Can we combine the results in the same database: YES / NO

- If YES – good, do it!
- If NO can we **fix** the problem
  - At the lab level
  - At the manufacturer level

  - If NO, can we **manage** the problem

“Combining Results”

- What does this mean?

- What criteria do we use?

Reporting “on the same line”

Thanks to Auckland Regional Quality Assurance Group (ARQAG)

Combining results

All assays close enough?

	Day 1 Lab 1	Day 2 Lab 2	Day 3 Lab 3	Day 4 Lab 2	Range
Sodium	135	137	136	134*	**135-145**
Potassium	4.5	4.7	4.9	3.8	**3.5-5.0**

Are the reference intervals suitable for all the results

Not Combining Results

	Day 1	Day 2	Day 3	Day 4	
	Lab 1	Lab 2	Lab 3	Lab 2	Range
Sodium	135	137	136	134*	**135-145**
Potassium	4.5	4.7	4.9	3.8	**3.5-5.0**
Troponin I (Centaur)	0.15*	…	…	0.08*	**<0.04**
Troponin I (Dade)	…	0.22*	…	…	**<0.10**
Troponin T	…	…	0.10*	…	**<0.001**

Combining results?

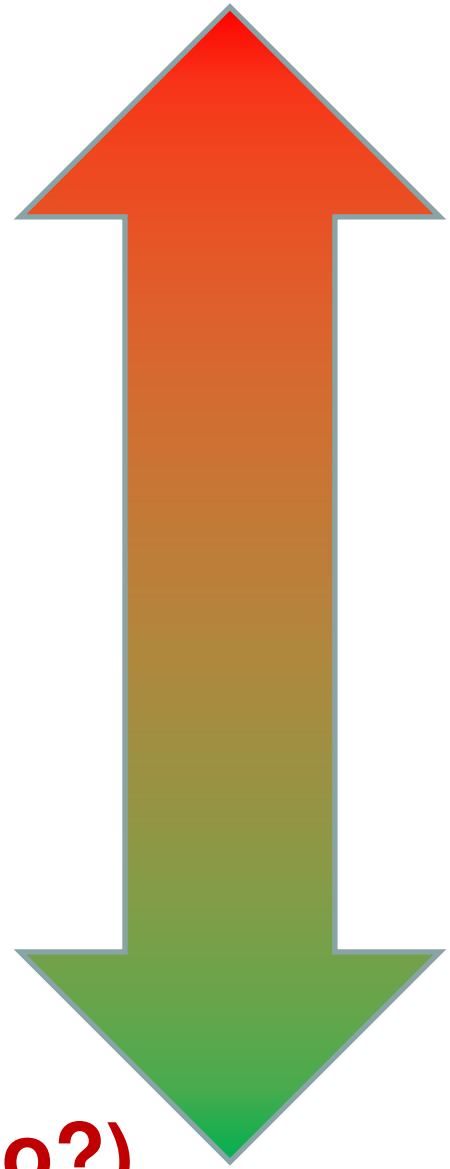
	Day 1 Lab 1	Day 2 Lab 2	Day 3 Lab 3	Day 4 Lab 2	Range
Sodium	135	137	136	134*	**135-145**
Potassium	4.5	4.7	4.9	3.8	**3.5-5.0**
Troponin I (Centaur)	0.15*	…	…	0.08*	**<0.04**
Troponin I (Dade)	…	0.22*	…	…	**<0.10**
Troponin T	…	…	0.10*	…	**<0.001**
Albumin (BCG)	45	42	…	42	**40-52**
Albumin (BCP)	…	…	38		**35-50**

Are these really different?

Do these intervals reflect the assays?

Combining Data - Criteria

- Can monitor patients (CVi)
  - Optimal, desirable, minimal
- Can diagnose (CVg)
  - Optimal, desirable, minimal
- State of the art
- Clear analytical differences
  (LDH, Amylase, troponin I)
- Specificity differences
  (Tumour markers)



Lumping and Splitting (by who?)

Combining Data - Criteria

- Quality standards
- Two sequential results in a database:
  - Can we use them to monitor a patient?
  - Can we use same criteria as for one lab?
  - Can we use same diagnostic decision points?

We need quality standards with "meaning"

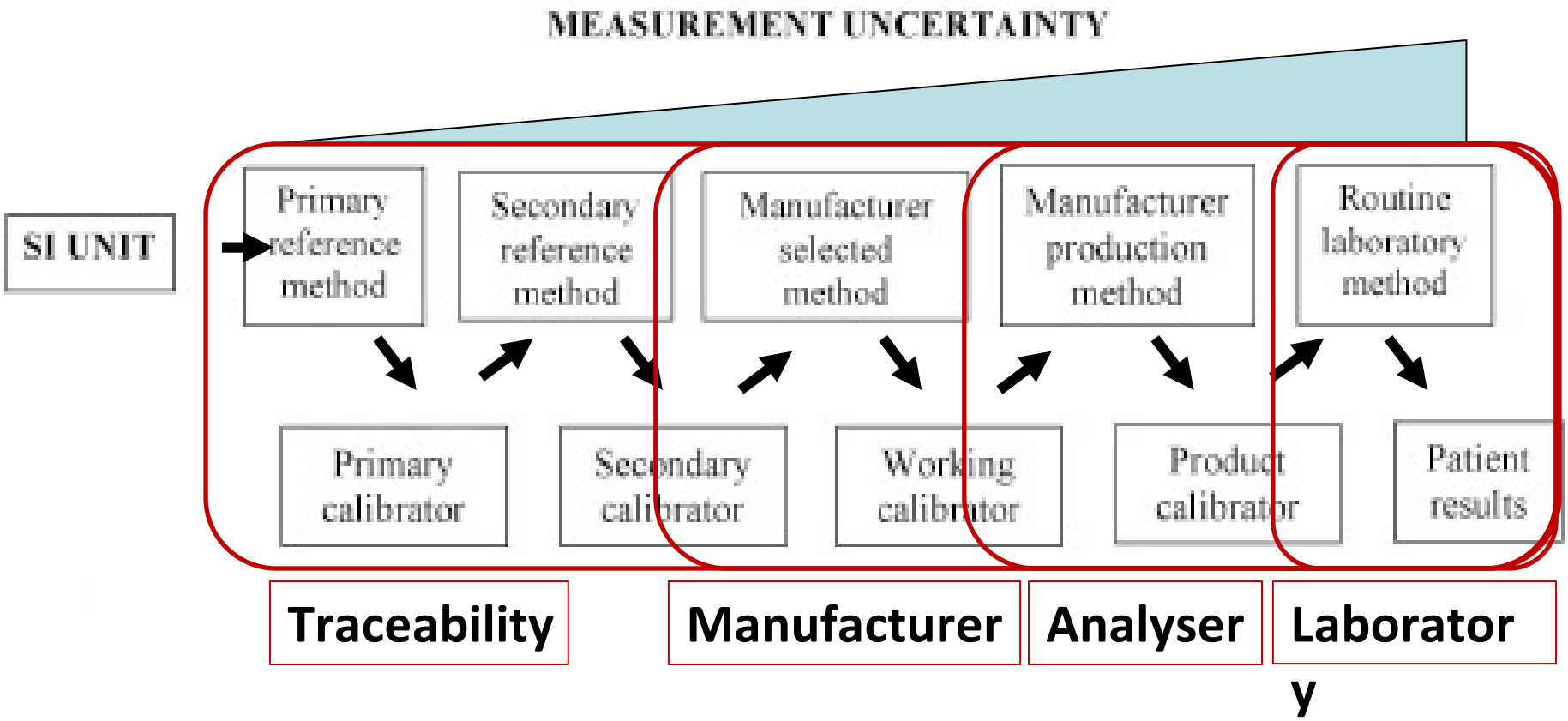
Can we communicate this meaning?

Lumping and Splitting

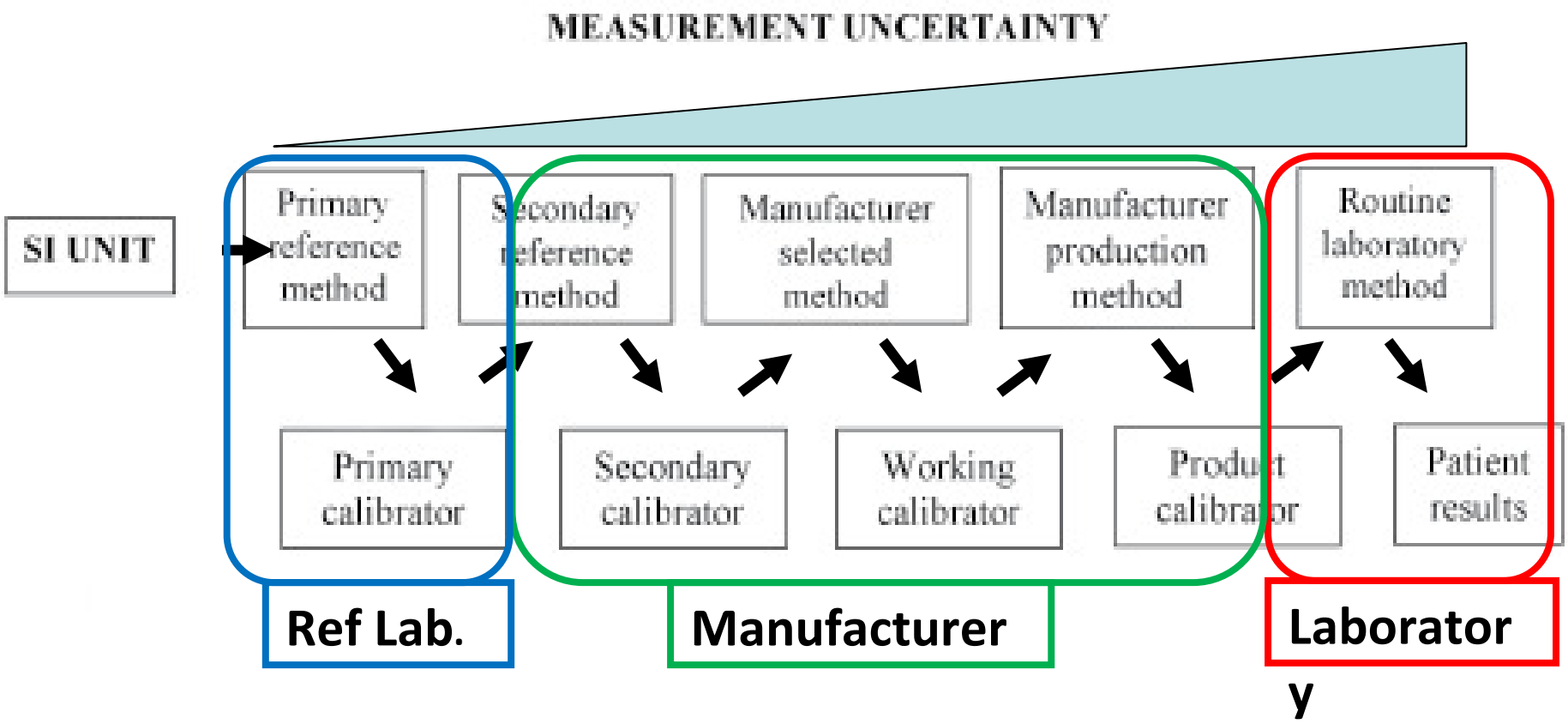
Can we combine results:

- All from all sources
- All with the same traceability
- All results from the same manufacturer
- All from the same analyser
- All from the same laboratory network
- All from the same laboratory

Traceability



Traceability



National or regional organisation

Important Paper

State of the Art in Clinical and Anatomic Pathology

State of the Art in Trueness and Interlaboratory Harmonization for 10 Analytes in General Clinical Chemistry

W. Greg Miller, PhD; Gary L. Myers, PhD; Edward R. Ashwood, MD; Anthony A. Killeen, MD, PhD; Edward Wang, PhD; Glenn W. Ehlers, BS/MT, MBA; David Hassemer, MS; Stanley F. Lo, PhD; David Seccombe, MD, PhD; Lothar Siekmann, PhD; Linda M. Thienpont, PhD; Alan Toth, BS

***Arch Pathol Lab Med.* 2008;132:838–846**

Miller et al

Table 3. Peer Groups With Excessive Bias Versus a Reference Measurement Procedure (RMP)

Analyte	RMP Values	Peer Groups, No.	Groups With Significant Bias ($P < .001$), %	Groups With Biases Greater Than Biologic Variability Criteria, %		
				Optimum	Desirable	Minimum
Bilirubin	0.36 mg/dL	45	48.9	60.0	51.1	35.6
Chloride	104 mEq/L	30	70.0	86.7	80.0	60.0
Glucose	98.5 mg/dL	32	40.6	28.1	12.5	0.0
Iron	65.4 mg/dL	30	56.7	33.3	10.0	0.0
Magnesium	1.59 mEq/L	25	56.0	88.0	64.0	56.0
Phosphate	3.25 μg/dL	29	89.7	93.1	48.3	20.7
Potassium	4.38 mEq/L	29	62.1	48.3	3.4	0.0
Sodium	140.7 mEq/L	31	67.7	90.3	77.4	67.7
Urea nitrogen	12.18 mg/dL	27	85.2	88.9	70.4	14.8
Uric acid	5.38 mg/dL	22	68.2	31.8	4.5	0.0

Glucose, Iron, Potassium, Urate: Can combine results and use common reference intervals

Miller et al

- Some assays already have very low between-method differences
- ***Can*** **combine results**
- ***Can*** **use common reference intervals**
  - Provided the people are the same
- Some are not at that stage
  - Need to work to achieve this goal

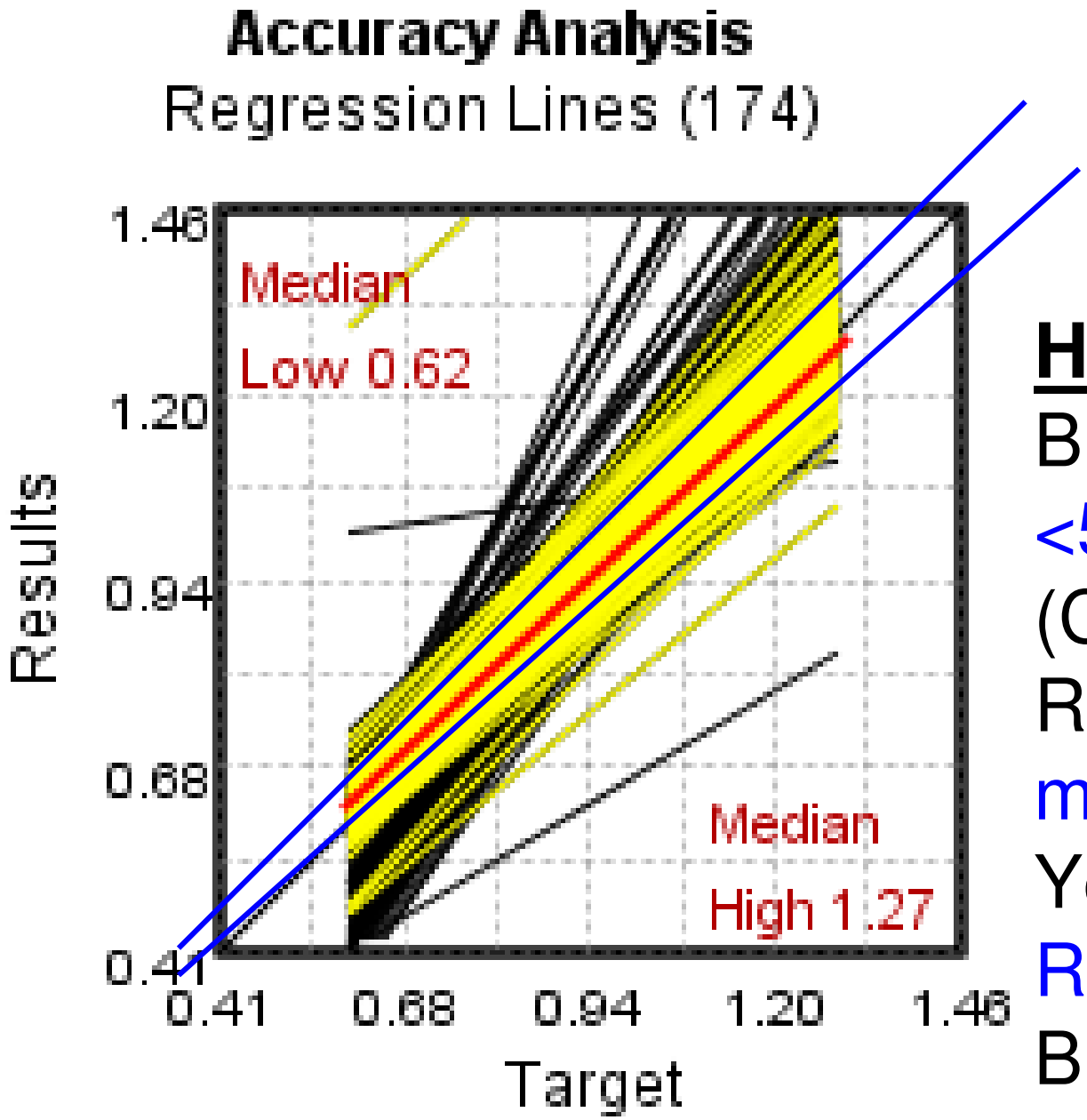
Are we responding to data that already exists?

Whose job is it?

WITHIN-METHOD BIAS ASSESSMENT USING QAP DATA

Graham Jones and Jan Gill

RCPA QAP - Adelaide



HDL

Bias standard: <5%

(CDC)

Red line: method mean

Yellow Lines: Roche Hitachi

Blue lines: + / - 5%

Bias within minimal limits

TEST	Hitachi Roche	Cobas Roche	Beckman coulter	Abbott	Olympus	Ortho	Bayer Siemens	Dade Siemens	Method Average
Sodium	65%	61%	58%	47%	58%	75%	77%	54%	**62%**
Magnesium	49%	70%	79%	67%	75%	54%	75%	72%	**68%**
Creatinine	86%	82%	41%	89%	47%	68%	64%	90%	**71%**
Bicarbonate	56%	67%	80%	44%		79%	88%	75%	**70%**
chloride	72%	75%	78%	71%	82%	86%	81%	78%	**78%**
lactate	92%	87%	52%			92%			**81%**
protein	80%	87%	51%	96%	91%	77%	100%	90%	**84%**
Calcium	85%	84%	78%	91%	97%	84%	75%	90%	**85%**
Cholesterol	72%	88%	97%	98%	79%	72%	100%	91%	**87%**
HDL Cholesterol	80%	84%	69%	95%	81%	95%	100%	98%	**88%**
albumin	81%	89%	93%	57%	100%	94%	100%	98%	**89%**
phosphate	98%	98%	45%	100%	100%	97%	100%	100%	**92%**
potassium	94%	98%	92%	71%	100%	100%	100%	94%	**94%**
transferrin	89%	93%	100%	100%	100%	89%	100%	83%	**94%**
urea	99%	100%	87%	100%	100%	100%	93%	100%	**97%**
iron	98%	100%	100%		100%	100%	100%	86%	**98%**
urate	98%	99%	100%	88%	100%	100%	100%	100%	**98%**

Analytes able to meet criteria

TEST	Method Average
phosphate	92%
potassium	94%
transferrin	94%
urea	97%
iron	98%
urate	98%

Individual methods able to meet sharing criteria

Actions:

- **Laboratories: outliers take action**
- **Other: able to share results and ref. intervals**

Analytes unable to meet criteria

TEST	Method Average
Sodium	62%
Magnesium	68%
Creatinine	71%
Bicarbonate	70%
chloride	78%

Individual methods unable to meet sharing criteria

Actions:

- **Individual laboratories: check bias and respond**
- **Manufacturers: improve calibration processes**
- **Other: wider reference intervals**

Quality Standards for Reference Laboratories

- Currently devised as a fraction of “field” Quality Standards
- Eg RELA limits of equivalence
- Note:
  - Very different field standards
  - Very different criteria
    - Regulatory
    - Statistical
    - Clinical

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)

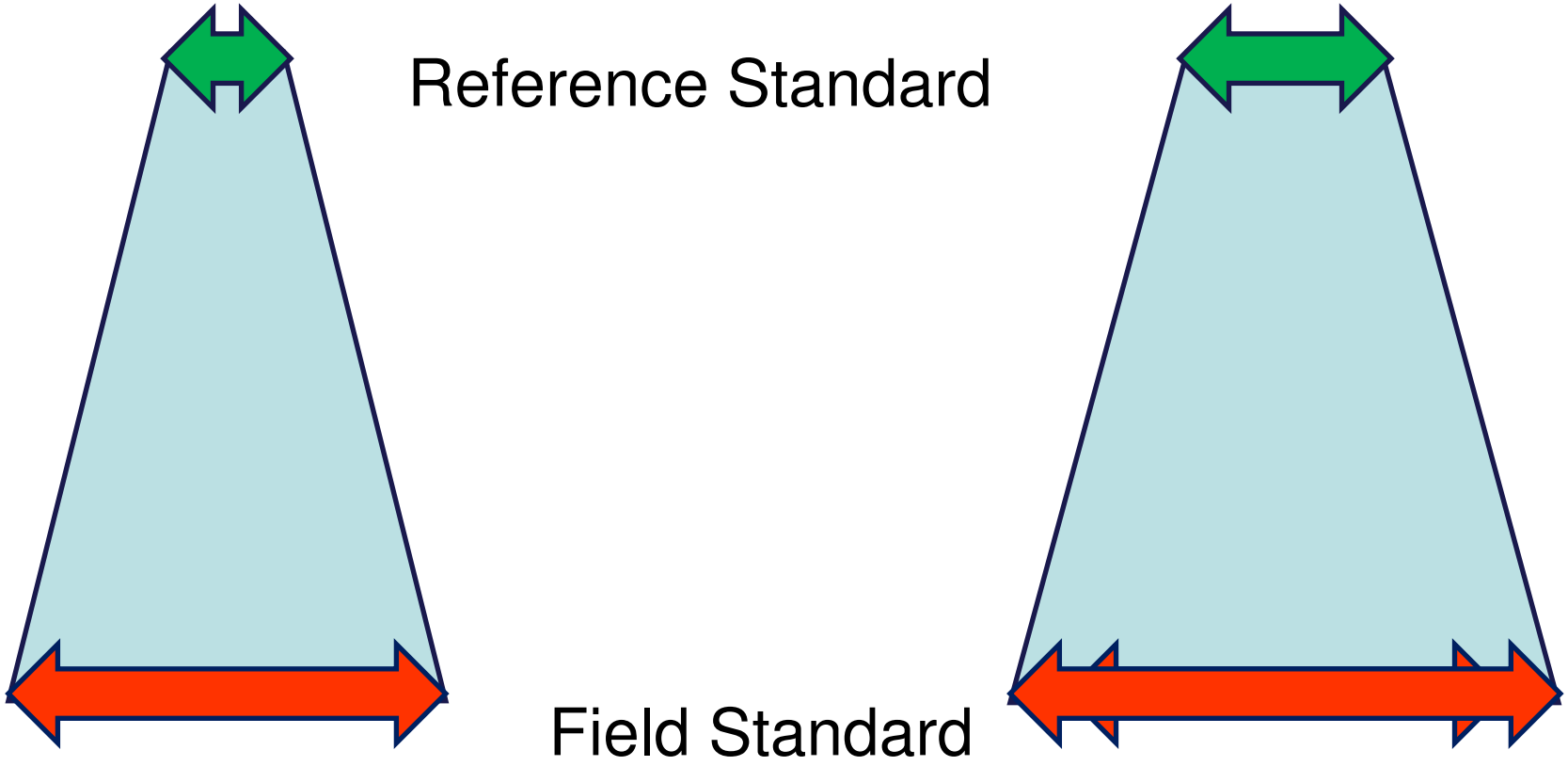
	Cholesterol	P_i	Lithium	Lactate dehydrogenase	Urate	Alkaline phosphatase	Amylase
Denmark	8.1	12.0	–	12.0	13.0	10.0	11.0
Netherlands	8.1	–	5.0	3.0	10.0	8.0	10.0
Belgium	8.4	14.0	10.0	15.0	15.0	10.0	17.0
Germany[a]	18.0	15.0	12.0	21.0	18.0	21.0	21.0
Finland	5.0	5.0	5.0	10.0	5.0	10.0	10.0
Switzerland	3.0	10.0	6.0	15.0	10.0	15.0	20.0
Croatia	10.0	10.0	–	20.0	10.0	20.0	–
Lithuania	7.0	5.0	–	7.0	7.0	7.0	10.0
United Kingdom	7.6	7.8	11.0	13.0	7.7	15.0	11.0
Spain	9.8	12.0	22.0	17.0	15.0	22.0	56.0
Italy	5.5	9.5	–	10.0	8.0	18.0	–
France	16.5	–	10.0	20.0	16.0	20.0	25.0
Portugal	5.0	8.0	–	16.0	9.0	29.0	–

Australia	5.0	10.0	8.0	15.0	7.8	15.0	15.0
CLIA	10.0		20.0	20.0	17.0	30.0	30.0
Range:	3-18	5-14	5-22	3-21	5-18	7-30	10-56

EQA Quality standards

- **How good we are:** **Outliers identified**
  - Statistical
  - +/- 2SD
  - 95th centile
- **How bad we don't want to be:** **Exclude poor labs**
  - Current state-of-the-art, and then some
  - Regulatory programs
- **How good we want to be:** **Promote improvement**
  - Biological variation
  - Established clinical criteria

Reference Quality Standards



Quality of reference standard may affect field standards
Eg Reference interval for serum sodium

RCPA QAP

General Serum Chemistry & Therapeutic Drugs Program

REVISION OF ALLOWABLE LIMITS OF PERFORMANCE

23 August 2010

RCPA Quality Assurance Programs Pty Limited
ABN 32 003 520 072

Chemical Pathology

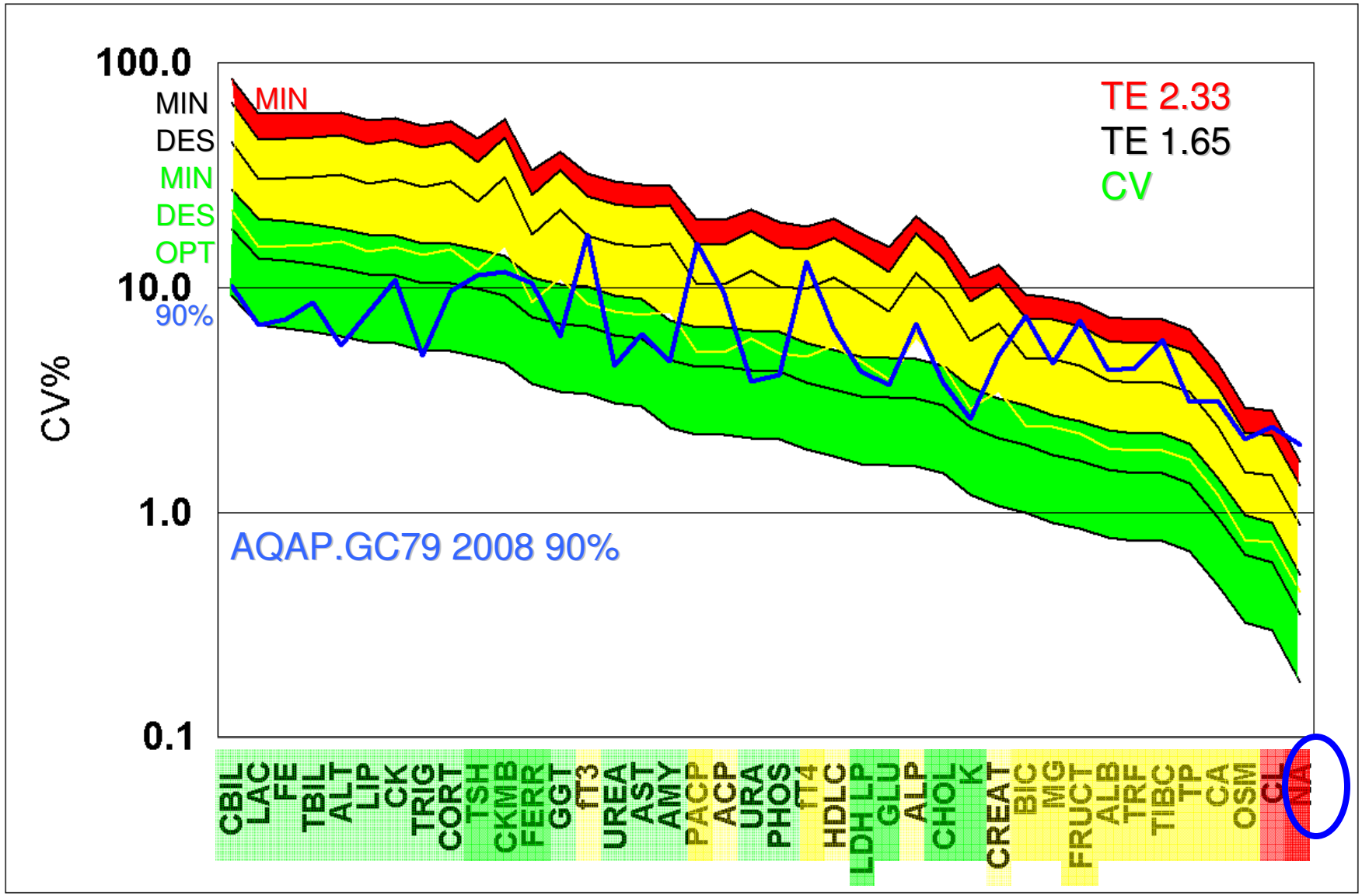
In association with the Australasian Association of Clinical Biochemists

RCPA QAP

- Allowable Limits of Performance (ALP)
- “Quality Standard”
- Clinically based
  - Previously “expert opinion”
- Revised 2010
- Hierachy:
  - Monitoring (CVi): optimal, minimal, desirable
  - Diagnosis (CVg+CVi): opt, min, desirable
  - Need about 80% of labs to reach criteria

Quality Standards with Meaning

RCPA QAP - Performance



RCPA QAP ALP

	Comment	Level	Basis
	Same	Optimal	Imprecision
	Same	Minimal	Imprecision
	Same	Minimal	Total Error
	Looser	Desirable	Imprecision
	Looser	Desirable	Imprecision
	Tighter	Optimal	Imprecision
	Tighter	Minimal	Imprecision
	Same	Desirable	Imprecision

42 ana
Limits
- loosened in 8 (19%)
- largely unchanged in 13 (31%)

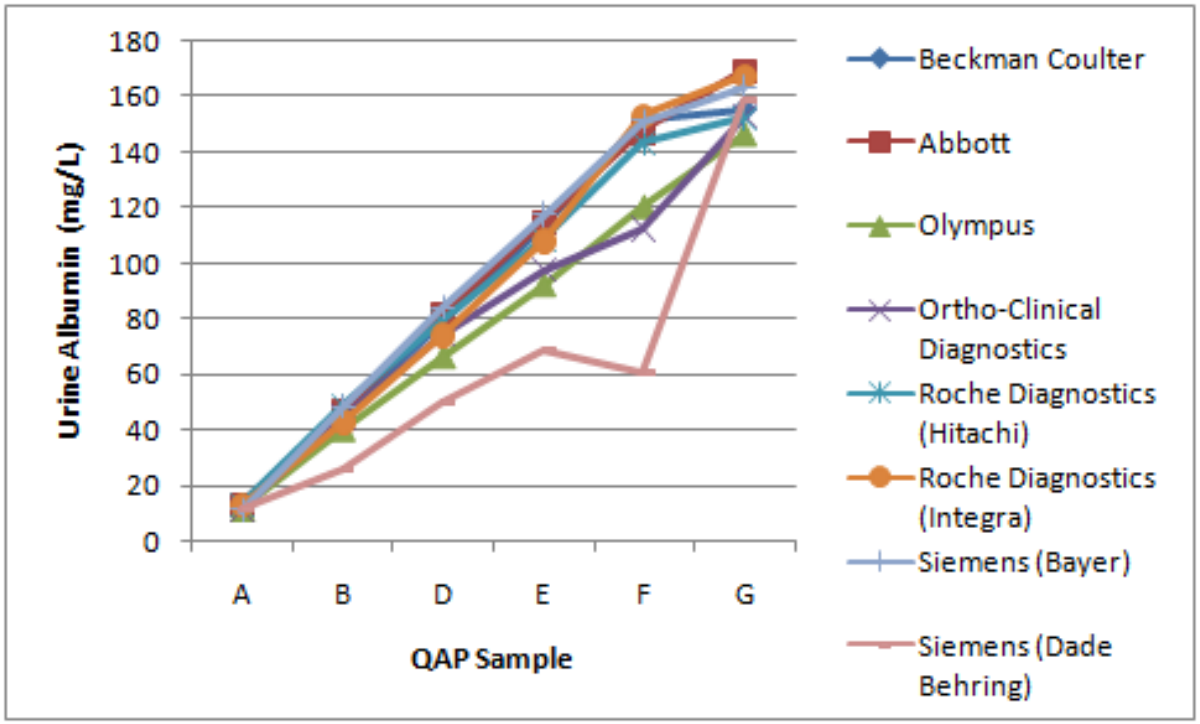
Reference Intervals – Alb Cr Ratio

Upper Ref. Limit	Number
1.0 mg/mmol	6
2.0 mg/mmol	2
2.5 mg/mmol	4
2.5 (m) / 3.0 (f)	1
2.5 (m) / 3.5 (f)	7
3.0 mg/mmol	1
3.5 mg/mmol	10

Highest over 3 x lowest

Reference Interval Differences

- Different assays?
  - Not related to assays (from Survey)
  - No evidence of assay Difference

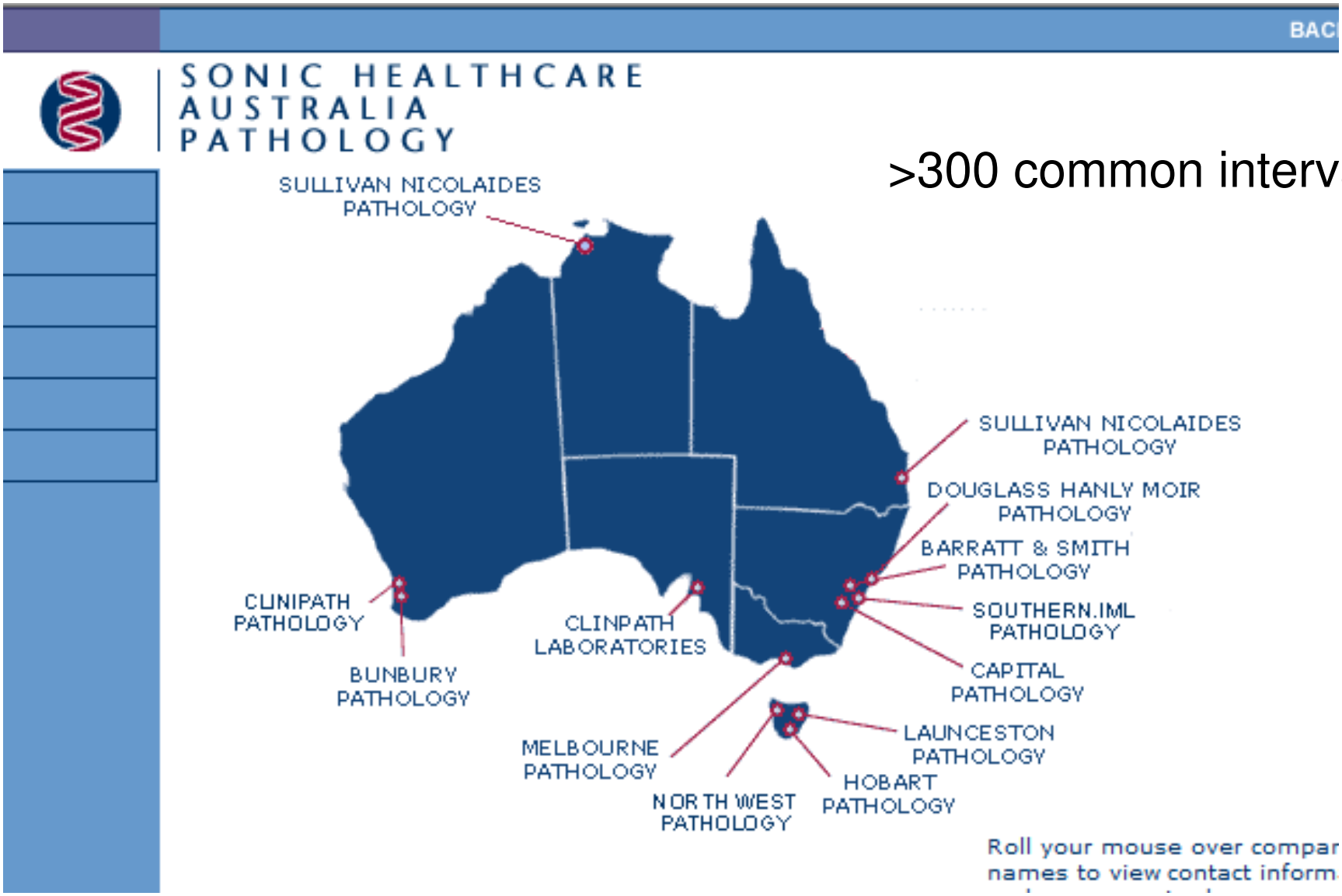


RCPA QAP Urine Albumin 2009 data

Common Decisions

- **Units, reference intervals, Quality specifications, lumping and splitting**
- **Australasian Groups**
  - **Units for drug measurements**
  - **Creatinine, eGFR**
  - **Urine albumin, protein**
  - **HbA1c units and diagnosis**
  - **Serum urate reporting**
- **RCPA, AACB, clinical organisations**

Sonic Healthcare



>300 common intervals

Summary

- Analytical variability does affect **patient care**
- QA can measure the variability, but **action** is required to fix or manage it
- Action needed at all the usual levels ...
- For communal activities, **communal action** is required
- Quality standards ⟷ Clinical use