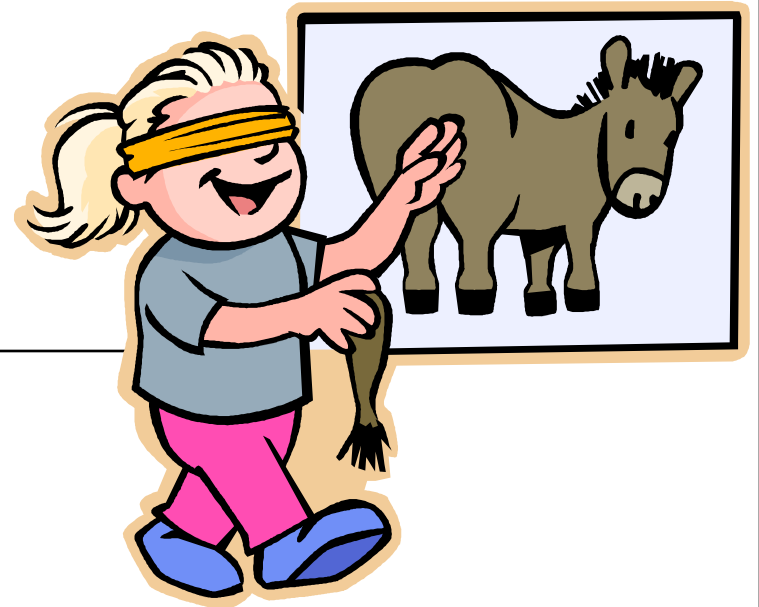


# Quality Assurance

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Ronda Greaves





# Outline

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- Internal Quality Control
- External Quality Assurance
- Biological Variation
- Uncertainty of Measurement (MU)



# AIM

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**The right result**

**From the right test**

**At the right time**

**On the right specimen**

**From the right patient**

**Interpreted using the right reference data**

# What is Quality?

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“Degree of excellence”

“Faculty, skill, accomplishment”

“High rank”



# What is Quality Control?

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- Quality Control in the medical laboratory is a system designed to increase the probability that each result reported is valid and can be used with confidence by the physician making a diagnostic or therapeutic decision.

# What is a Control?

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- A control is a “**Patient-Like**” sample that is composed of one or many constituents whose concentrations are known.
- When the observed control values fall within the acceptable ranges, the laboratory can confirm the test system is **working properly** and the patient results can be reported with **confidence**.
- Provides a **method for evaluating new tests** reagents, instruments or personnel.
- To **develop historical records** of the testing systems for comparative purposes.



**Internal QC and External QA**

# Internal Quality Control

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Monitors the device by testing a control material with a known value and limits

Tells you immediately whether the device is reliable to test patients



## ISO 15189: 2003(E), subclause 5.6.1

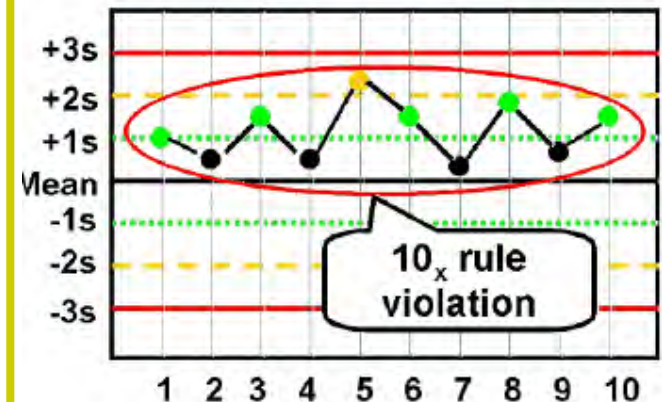
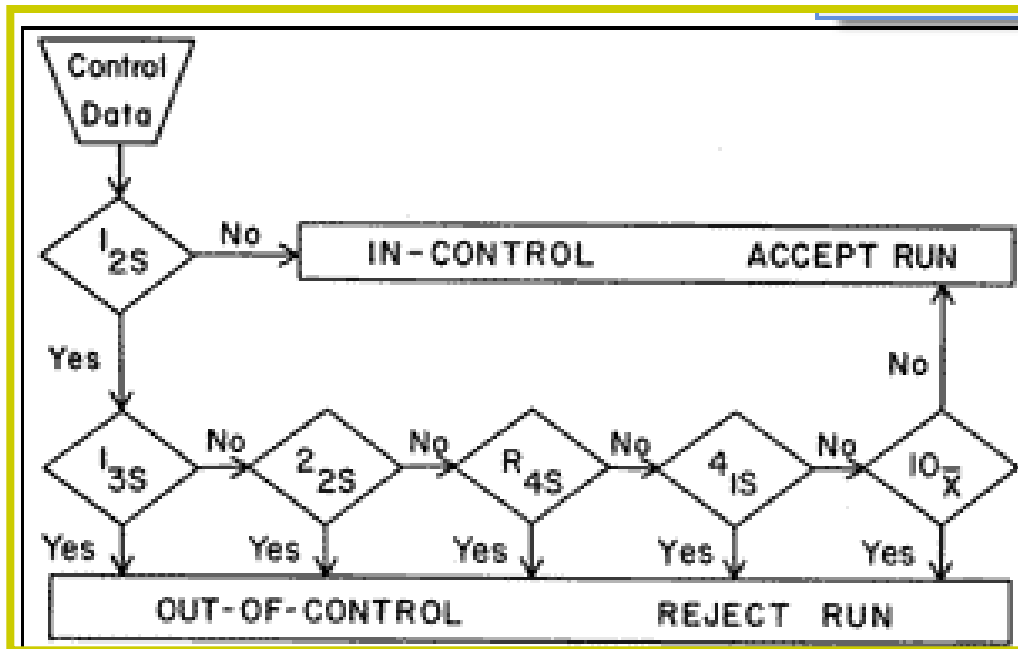
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“The laboratory shall design internal quality control systems that verify the attainment of the internal quality of results. It is important that the control system provide staff members with clear and easily understood information on which to base technical and medical decisions...”

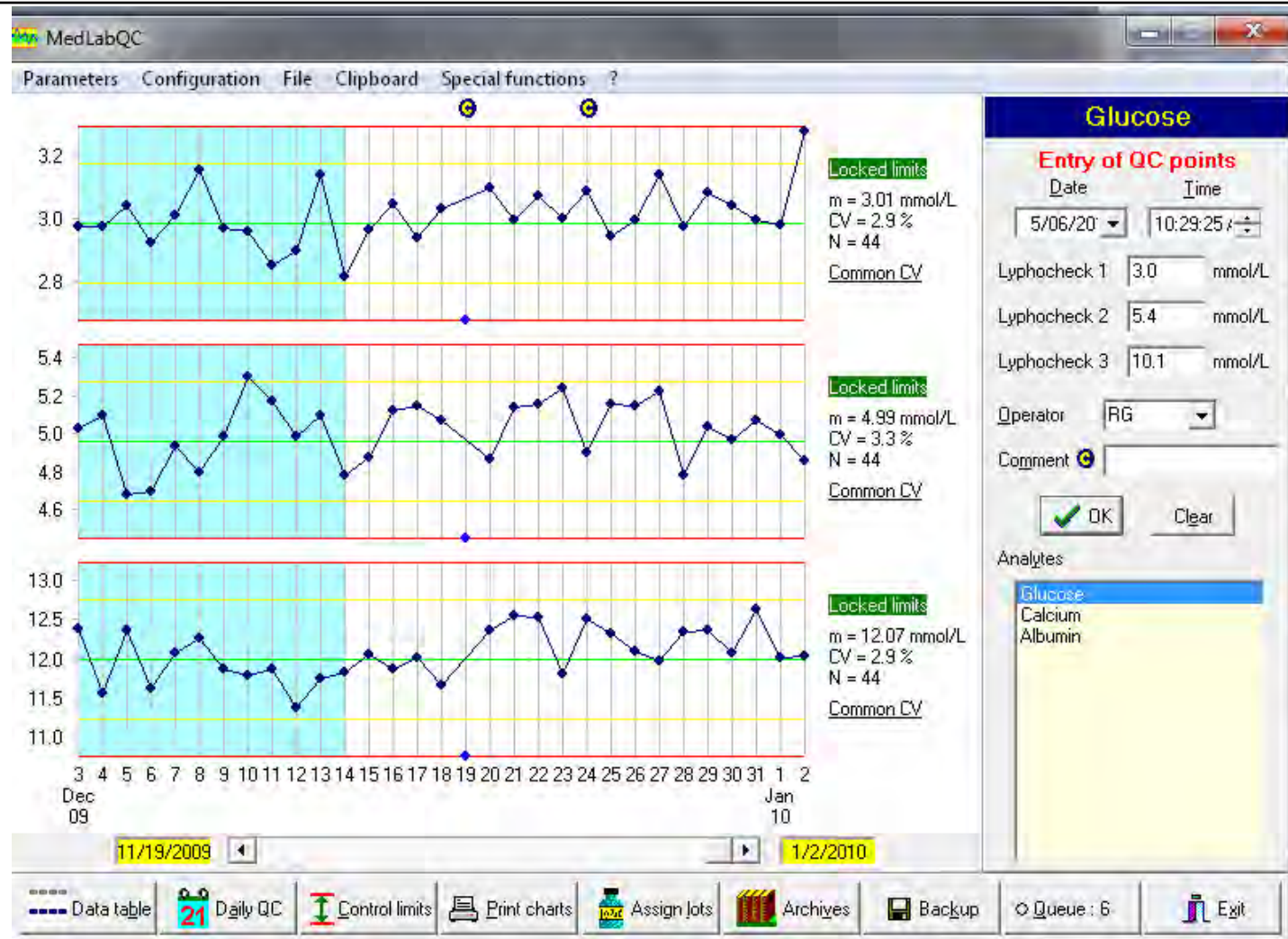


# Westgard Rules = Multirule QC

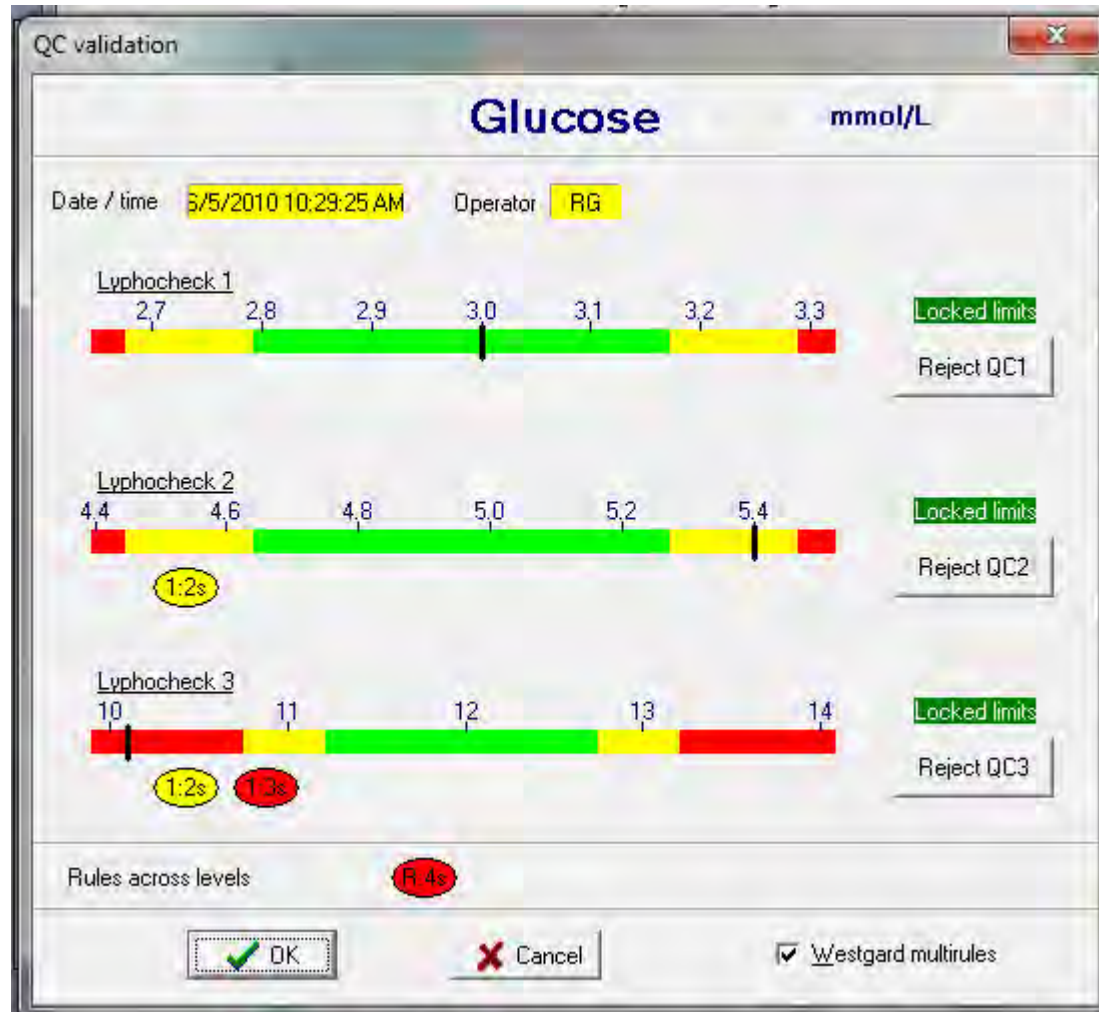
- Combination of decision criteria, or control rules, to decide whether an analytical run is in-control or out-of-control.



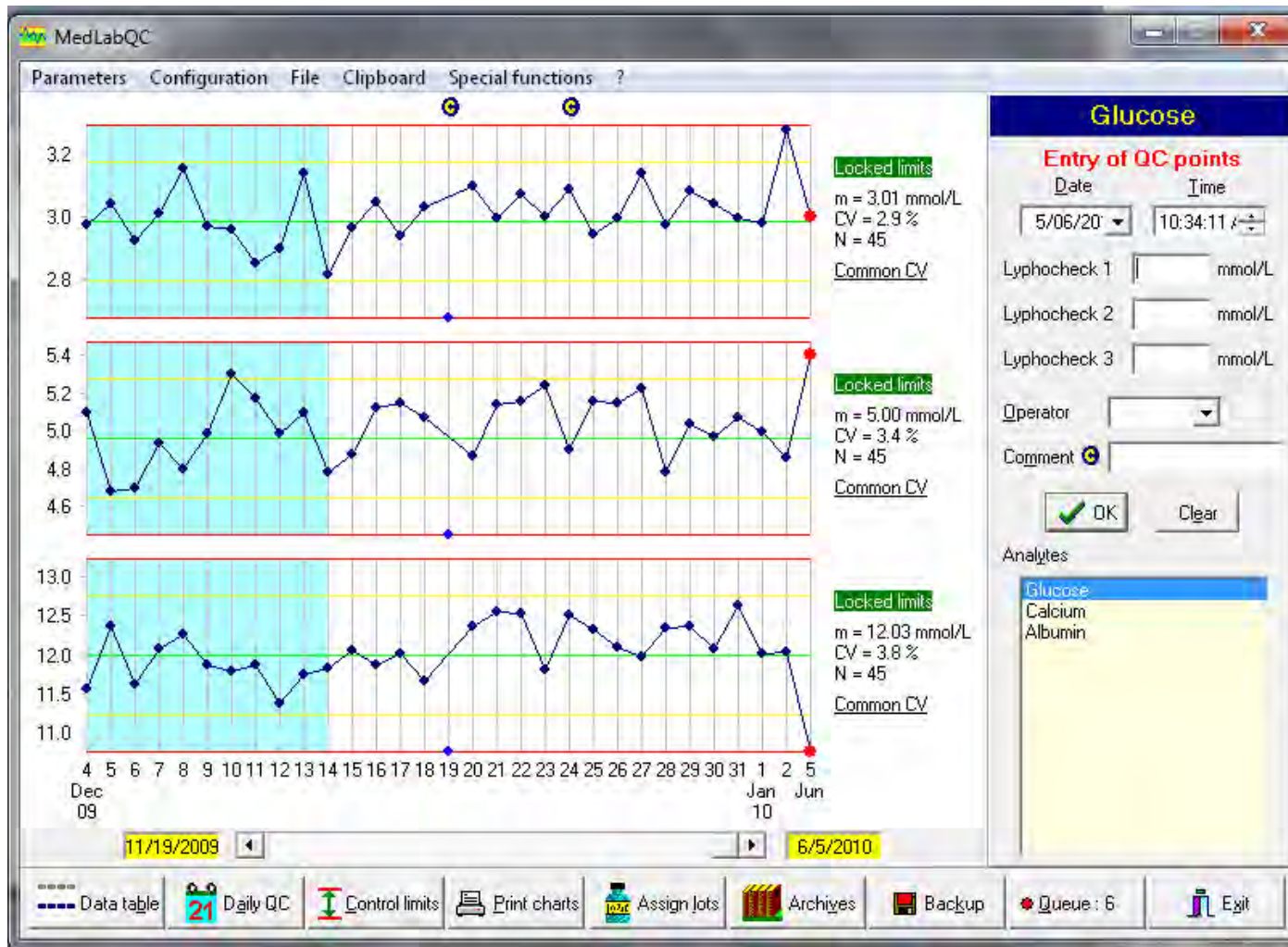
# MedLabQC - 1



# MedLabQC – 2: Westgard rules applied

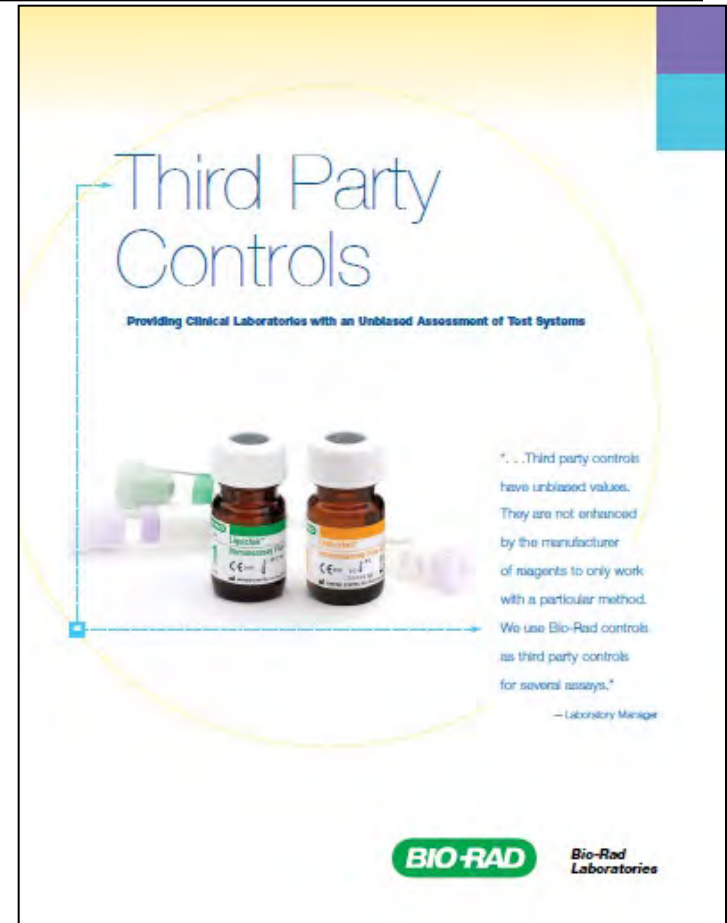


# MedLabQC - 3



# Third Party Controls

- Not optimized for a specific test, kit, reagent system or instrument.
- Independent of Reagent and Kit Lot Changes
- Not “Optimized” for Specific Manufacturer
- “Patient Like”
- E.g. Bio-Rad, Utak, MAS



The advertisement features a central image of two small brown vials with white caps and labels, placed on a white surface. A blue dashed line forms a rectangular frame around the vials, with arrows pointing from the text to the vials. The background is white with a yellow and blue gradient at the top. The Bio-Rad logo is in the bottom right corner.

**Third Party Controls**

Providing Clinical Laboratories with an Unbiased Assessment of Test Systems

"... Third party controls have unbiased values. They are not enhanced by the manufacturer of reagents to only work with a particular method. We use Bio-Rad controls as third party controls for several assays."

— Laboratory Manager

**BIO-RAD** Bio-Rad Laboratories

# Why is this important?

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- By using a third party control material, the laboratory is assured that the entire system is not compromised by using a product that may have been optimized to give predictable results.
- This is a **true test on the system.**
- Example:  
[http://www.paulgolding.id.au/THE\\_B12\\_BETRAYAL/PublicPages/ArroganceApathyGreed/Government/WhatQualityAssurance.html](http://www.paulgolding.id.au/THE_B12_BETRAYAL/PublicPages/ArroganceApathyGreed/Government/WhatQualityAssurance.html)

# External Quality Assurance

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# What is QA?

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- = external quality assurance (EQA)
- = external quality assessment (EQA)
- = proficiency testing scheme
  
- An external program allows sites to check the quality of their results in comparison to other sites by testing an identical sample with an unknown value



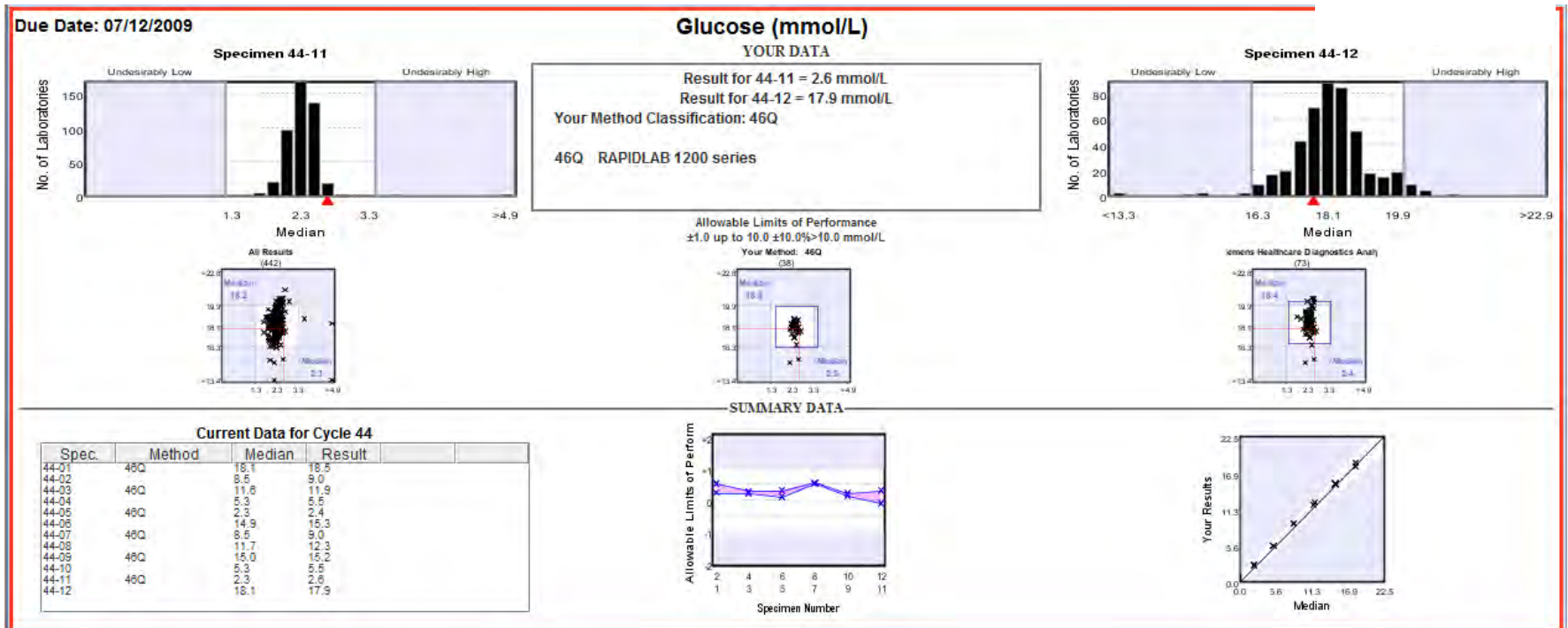
# ISO 15189 application document

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## 5.6.4 Proficiency testing (External quality assurance programs (QAPs))

- (i) Where available, a program which includes other laboratories in the country / region is preferred as this optimises the opportunity to reduce between-laboratory variation such as may be seen in a patient using multiple laboratories.
- (ii) Where analysers (e.g. blood gas analysers) are located outside the laboratory these must be enrolled separately in a QAP unless they meet the requirements of Appendix B.
- (iii) Regular submission of results to the program organisers is required whether or not the timing coincides with the testing of patients' samples.
- (iv) On receipt of returns from the program organisers it must be ensured that:
  - a) QAP performance is reviewed and discussed by the person in charge (as defined by NPAAC) and all relevant staff;
  - b) there is evidence that the review has taken place; and
  - c) the implication of unsatisfactory QAP performance for patient results must be considered and a record of the considerations and action taken kept.
- (v) As far as practicable, QAP samples must be treated in the same way as patients' samples. Additionally, all staff (including part-time and evening staff) involved in testing patients' samples should participate in the QAP where possible with records kept.

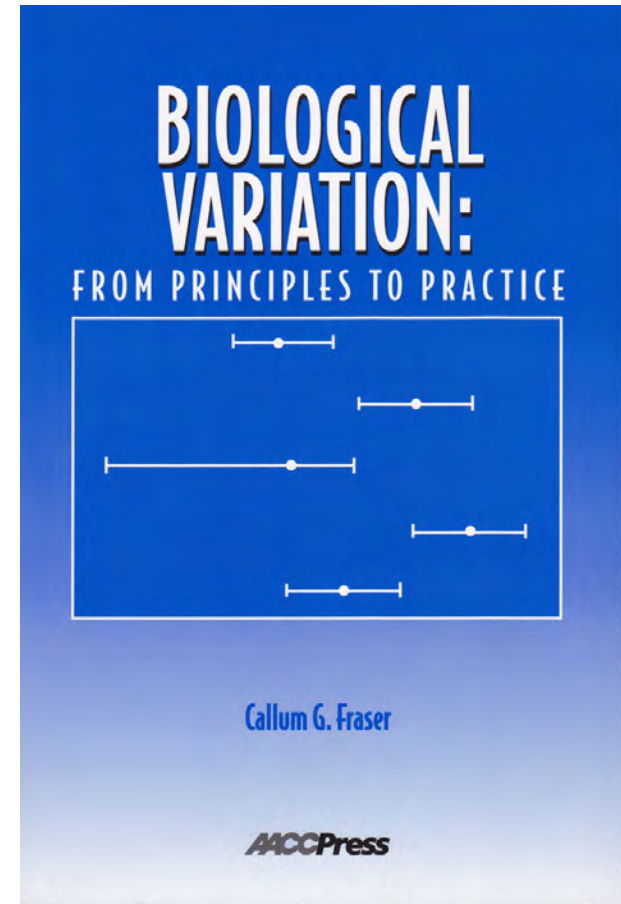
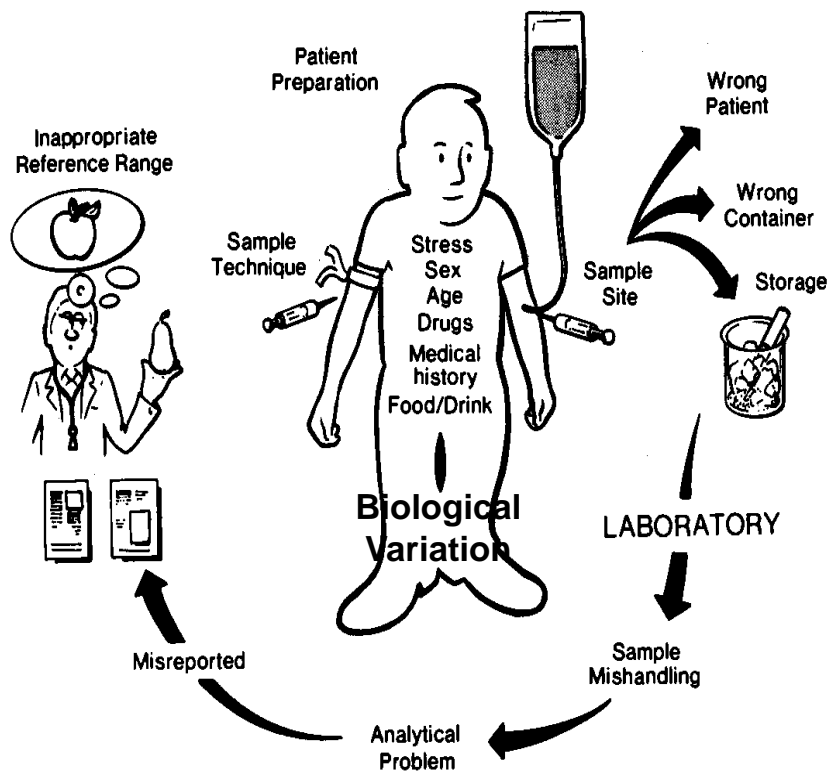
# Example EQA data



# Biological Variation

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# Biological Variation



## **Biological variation database, and quality specifications for imprecision, bias and total error (desirable and minimum). The 2010 update**

**CARMEN RICÓS,<sup>1,2</sup> JOSÉ-VICENTE GARCÍA-LARIO,<sup>1,3</sup> VIRTUDES ALVAREZ,<sup>1,4</sup> FERNANDO CAVA,<sup>1,5</sup> MARIVI DOMENECH,<sup>1,6</sup> AMPARO HERNÁNDEZ,<sup>1,4</sup> CARLOS-VICTOR JIMÉNEZ,<sup>1,7</sup> JOANA MINCHINELA,<sup>1,7</sup> CARMEN PERICH,<sup>1,8</sup>, MARGARITA SIMÓN,<sup>1,9</sup> CARMEN BIOSCA,<sup>1,10</sup> PILAR FERNÁNDEZ-CALLE<sup>1,11</sup>**

<sup>1</sup>Analytical Quality Committee, Spanish Society of Clinical Chemistry and Molecular Pathology (SEQC),

<sup>2</sup>Laboratori Clínic Hospital Universitari Vall d'Hebron (Barcelona),

<sup>3</sup>Hospital de Motril (Granada),

<sup>4</sup>Laboratori Clínic del'Hospitalet,

<sup>5</sup>Fundación-Hospital Alcorcón (Madrid),

<sup>6</sup>Laboratori Clínic Manso (Barcelona),

<sup>7</sup>Laboratori Clínic de Badalona,

<sup>8</sup>Laboratori Clínic Bon Pastor(Barcelona),

<sup>9</sup>Laboratori Intercomarcal Vilafranca del Penedès,

<sup>10</sup>Servei deBioquímica Hospital Germans Trias i Pujol (Badalona),

<sup>11</sup>Servicio AnálisisClínicos Hospital La Paz (Madrid)

- First presented at Stockholm international consensus conference on Strategies to Set Global Analytical Quality Specifications in Laboratory Medicine
- Scan J Clin Lab Invest 1999;59:475-586
- 2010: 6th edition comprising 319 analytes
- <http://www.westgard.com/biodatabase1.htm>

# Common Abbreviations

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- **CV<sub>w</sub> = within-subject biologic variation**
- **CV<sub>g</sub> = between-subject biologic variation**
- **CV<sub>a</sub> = actual analytical imprecision**
- **CV<sub>t</sub> = calculated total error**
- **I = desirable specification for imprecision**
- **B = desirable specification for inaccuracy**
- **TE = desirable specification for allowable total error**

# CV<sub>t</sub>

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- The combined estimate of analytical and biological variation (CV<sub>t</sub>) is expressed as:

$$CV_t = \sqrt{[(CV_a)^2 + (CV_w)^2]}$$

Fraser CG. Biological Variation: From Principles to Practice. AACCC Press. 2001.

- CV<sub>w</sub> = within-subject biologic variation
- CV<sub>a</sub> = actual analytical imprecision
- CV<sub>t</sub> = calculated total error

# CVa: Analytical Imprecision

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- Analytical imprecision should not contribute significant additional variation to the test result when compared with the natural variation of the analyte being measured.
- For a “healthy” individual the result of a test will differ from the previous one because of:

**Biological Variation of the analyte in the individual (CVi)**

+

**Analytical variation (Imprecision) of the method (CVa)**



MU

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Uncertainty of Measurement

# What is MU?

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- Uncertainty is numerical information that can complement a result, indicating the magnitude of the doubt about that result.
- The Uncertainty of Measurement (MU) provides a quantitative estimate of the quality of that test result.
- Spread of values normally expected when repeatedly measuring a property in the same specimen by a properly conducted test procedure (ie. SOP)
- The international standards ISO 15189 requires laboratories to provide estimates of their uncertainty for analytes that are measured.
- Relates to long term imprecision
- Bias not an additional uncertainty



# MU: Formal Definition

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**Terms and definitions**

**ISO 15189:2003(E)**

**3.17**

**uncertainty of measurement**

“a parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand”

[VIM:1993, definition 3.9]

# ISO 15189 application document

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## 5.6.2 Estimation of uncertainty of measurement

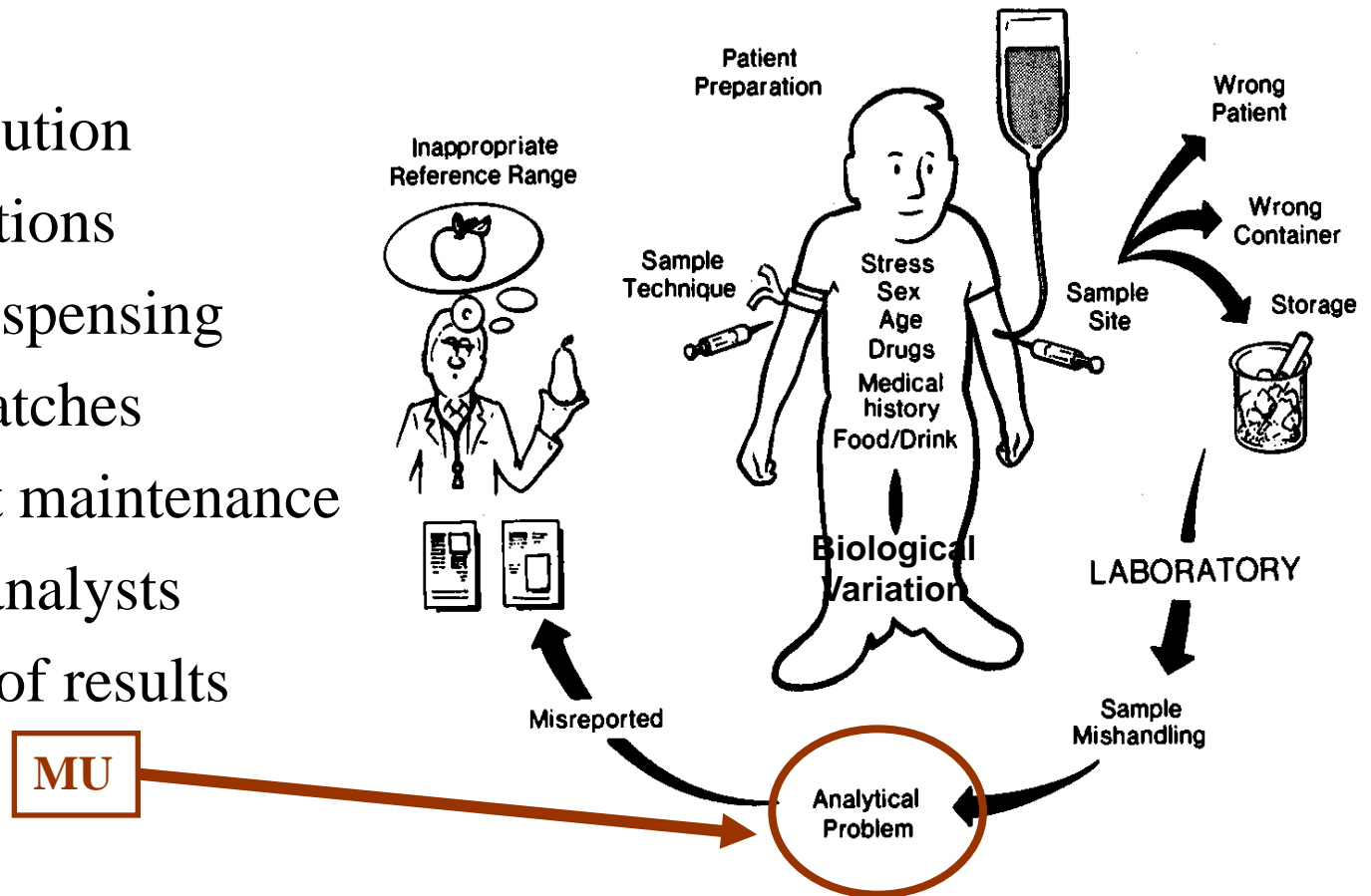
The estimation of uncertainty of measurement (MU) applies at present to quantitative tests only. This includes those tests where a numerical value is reported as a qualitative result, such as serological assays with a 'cut-off' value where the numerical result is reported as 'detected' or 'not detected'.

The following must be available:

- the procedure for estimating and reporting MU;
- examples of completed estimations using the laboratory's documented procedures; and
- a plan or schedule showing how the laboratory intends to achieve the estimation of the uncertainty of measurement for all relevant methods.

# What contributes to the MU of a method?

- Sampling
- Sample dilution
- Re-calibrations
- Reagent dispensing
- Reagent batches
- Instrument maintenance
- Different analysts
- Rounding of results
- Etc.



# A simple approach to calculate MU

- Define the analytes
  - n This is the measurand
- Internal QC
  - n Use at least 30 values to calculate the mean & CV at clinical decision point
- Expanded uncertainty =  $2 \times \text{CV}\%$ 
  - n i.e. – this given an indication of the 2 SD range
- Report MU

- Homovanillic acid
  - n Measured by HPLC
  - n Urine
- **Level 1 QC**
  - n **Mean = 51  $\mu\text{mol/L}$**
  - n **CV = 6%**
- **Expanded CV = 12%**
- **“For HVA concentration of approximately 51  $\mu\text{mol/L}$  the MU is  $\pm 6 \mu\text{mol/L}$  i.e. 45 – 57  $\mu\text{mol/L}$ .”**

# Is the assay fit for purpose?

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- The analytical goal for fitness for purpose for an assay is based on intra-individual biological variation ( $CV_w$ ) under the following criteria:
  - n Optimum:  $CV_a = < 0.25 \times CV_w$
  - n Desirable:  $CV_a = < 0.5 \times CV_w$
  - n Minimum:  $CV_a = < 0.75 \times CV_w$ .

White GH, Farrance I: Uncertainty of Measurement in Quantitative Medical testing – A Laboratory Implementation Guide. Clin Biochem Rev 2004;25: S1-4.

# Determine fitness for purpose with biological variation data.

## Example Vitamin A

- **Level 1 QC**
  - n **Mean = 1.3  $\mu\text{mol/L}$**
  - n **CV = 6.0%**
  - n **Expanded CV = 12.0%**
  - n **“For Vitamin A concentration of approximately 1.3  $\mu\text{mol/L}$  the MU is  $\pm 0.1 \mu\text{mol/L}$  i.e. 1.2 – 1.4  $\mu\text{mol/L}$ .”**

	Analyte	Biological Variation		Desirable specification		
		CVw	CVg	I(%)	B(%)	TE(%)
S-	Retinol	13.6	19.0	6.8	5.8	17.1

- **The fitness for purpose is assessed by the ratio of  $CV_a/ CV_w$** 
  - n **i.e.  $6.0/13.6 = 0.44$**
  - n **Vitamin A is within the “desirable” level of fitness for purpose.**





# What if CVa fails?

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- Identify/estimate/modify major contributors to analytical imprecision
- CVa may be fixed with automated systems
- Consider changing method

# Example Biological Variation study

Clinica Chimica Acta 393 (2008) 128–129



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journal homepage: [www.elsevier.com/locate/clinchim](http://www.elsevier.com/locate/clinchim)



Letter to the Editor

Total intra-individual variation in sweat sodium and chloride concentrations for the diagnosis of cystic fibrosis

Gus Koerbin<sup>a</sup>, Ronda F. Greaves<sup>b</sup>,  , Heather Robins<sup>a</sup>, Jodie Farquhar<sup>a</sup> and Peter E. Hickman<sup>a, c</sup>

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<sup>c</sup>ANU Medical School, Canberra, Australia

# SUMMARY

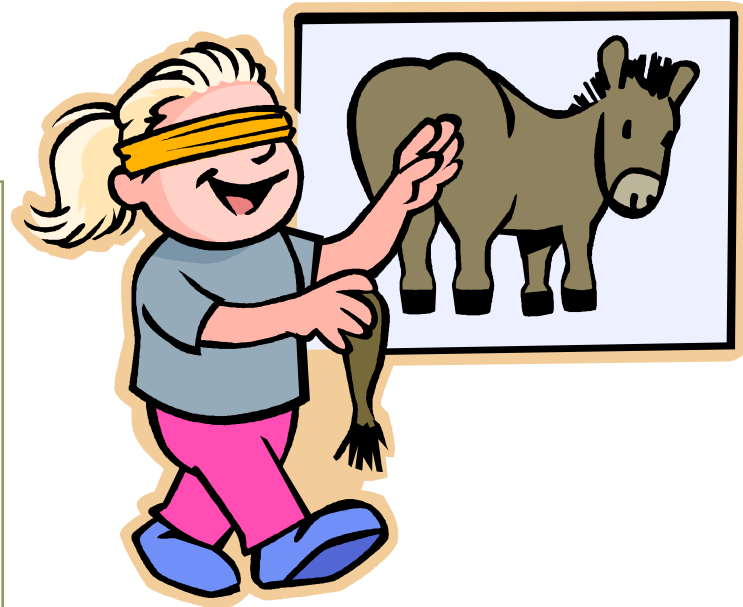
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# Why worry about Quality Goals?

- The machine has given you a result
- Of course this is correct!
- Is it?
- How do you know?

**ANSWER:** The probability of obtaining the correct result is increased when:

1. Internal and external QC are analysed and outliers are actioned
2. The assay is fit for purpose
3. Results are reported against appropriate reference intervals



# With QA we fulfil our aim

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**The right result**

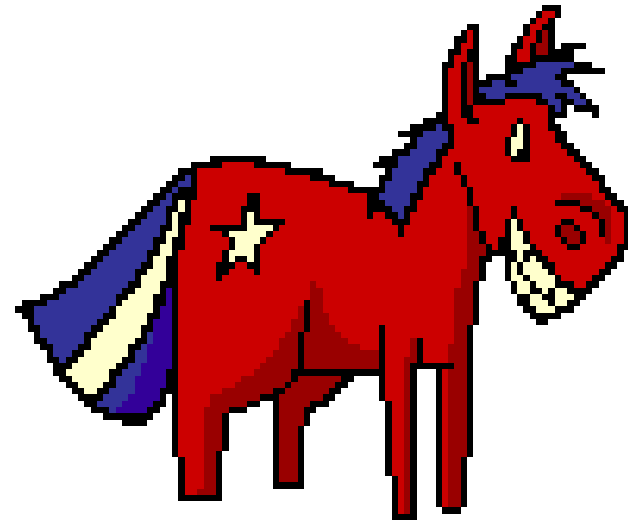
**From the right test**

**At the right time**

**On the right specimen**

**From the right patient**

**Interpreted using the  
right reference data**



MU will continue to evolve as a tool for defining assay  
imprecision and fitness for purpose