Trusting Numbers

A Hitch-hiker's Guide to Measurement Uncertainty in Laboratory Medicine

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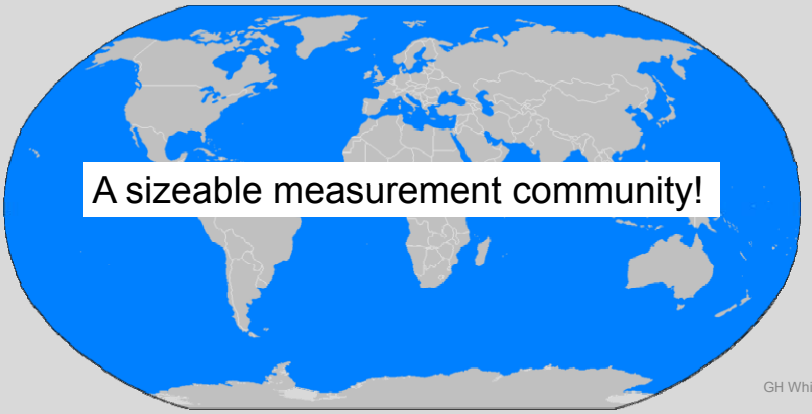
Medical laboratories:

Hundreds of different measurands

Many thousands of medical laboratories

Many millions of measurements/day



Measurement results

Diagnosis

Disease - severity

- prognosis

- management

Therapeutic drug monitoring

Screening – disease, health

Safety – surgery, procedures

Research

Positive impact on quality of life and death

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JCGM-WG1 template for reporting the comments on *JCGM 100:201X CD*

Member organization (M.O.) or NMI :...IFCC.....

Please, fill in the Table sequentially according to the text

M.O. or NMI	Serial item No.	(Sub) clause (e.g. 4.1)	Paragraph No. / Line No. / Figure/Table/Note	Justification for change	Proposed change	Response of JCGM-WG1
	1	6.10	Line 2	Expansion of BIPM abbreviation not correct	Give meaning of abbreviation in original language, with English equivalent in parentheses if desired	
	2					
	3					
	Etc.					

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ISO/IEC 17025

ISO - 15189:2007: Medical laboratories – Requirements for quality and competence

'The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase….'

Field-specific guidance on estimating MU not available

Accreditation Australia: Mandatory

2004:
Needed to develop a medical laboratory approach to MU
- based on ISO 17025, QUAM:2000 etc.

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Pathology Disciplines

Anatomical Pathology (Histopathology)
Clinical Chemistry – most prolific measuring discipline
Clinical Immunology & Allergy
Clinical Microbiology & Virology
Clinical Pharmacology
Haematology, Transfusion
Genetic Pathology

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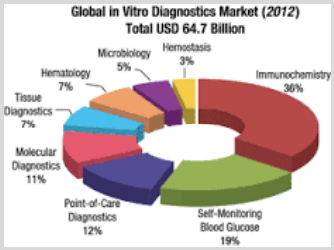
A tale of three cultures

Assume results have required quality

Total Error Approach deeply embedded

A costly business



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Introducing MU to Australian medical laboratories

Mascot for introducing a proposed revision of the GUM?

The “wound man”, indicating the various injuries from different weapons.
From the Grosse Wundartzney, of Paracelsus, 1536.

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ISO 15189:2007 - GUM not a normative reference

GUM:

1.4 It may be necessary to develop particular standards based on GUM that deal with the problems peculiar to specific fields…

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3.4.2 ..Because the …. model may be incomplete…evaluation of uncertainty can be based as much as possible on observed data.

3.4.2…..use of long-term quantitative data, …and control charts that can indicate if a measurement is under statistical control, should be part of the effort to obtain reliable evaluations of uncertainty.

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Routine medical laboratories

'Top-down approach' to MU well-suited

No need for developing/testing models of MPs

No need for GUM high level maths/statistics

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GUM – Can usefully apply basic principles

Definition of the quantity intended to be measured (measurand)

Comprehensive description of the measurement procedure

Elimination of known significant bias

Systematic and random uncertainties treated same way

Uncertainty of results expressed as an absolute or relative SD

Interval of values around a measured value within which the 'true' value believed to lie, with stated level of confidence

Measured value is best estimate

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MU for the routine medical laboratory

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Request-Test-Report-Cycle

Many sources of uncertainty

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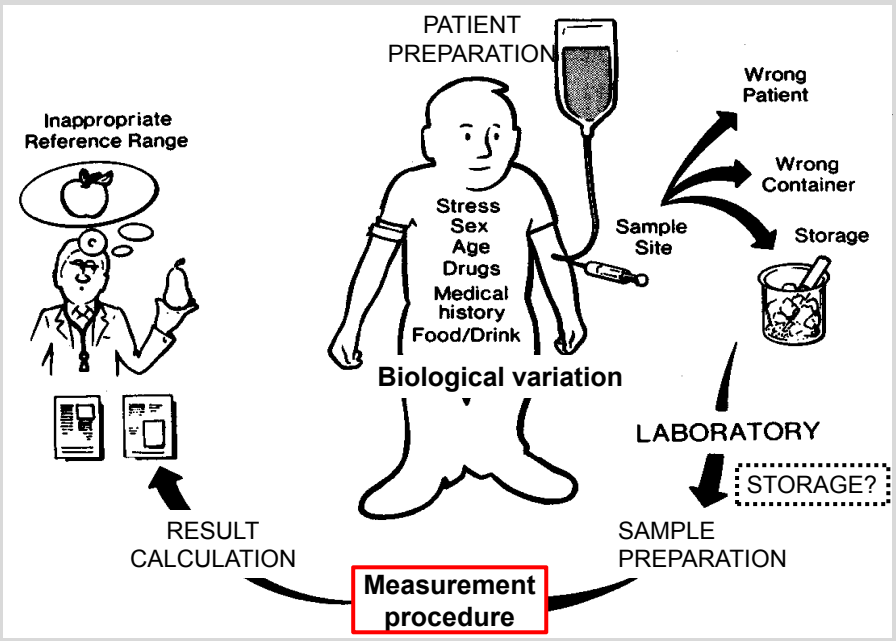

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MU only applies to technical bounds of MP

Most measurands are measured once in a patient sample

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How 'uncertain' can a patient result be, and still be clinically useful?

↓

How are results interpreted?

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Results are compared with:

- biological reference intervals
- clinical decision values
- previous results

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How sensitive are reference intervals to identifying normal/abnormal results?

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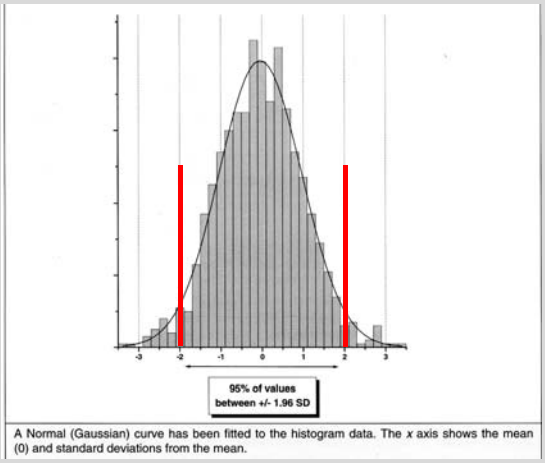
Reference intervals

Typically central 95% of 'healthy' values



A Normal (Gaussian) curve has been fitted to the histogram data. The *x* axis shows the mean (0) and standard deviations from the mean.

Excludes 2.5 % 'presumed healthy' at each end

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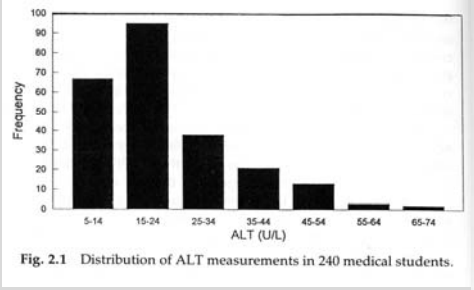

Fig. 2.1 Distribution of ALT measurements in 240 medical students.

From: Harris Ek, Boyd JC. Statistical Bases of Reference Values In Laboratory Medicine. Dekker Inc. 1995.

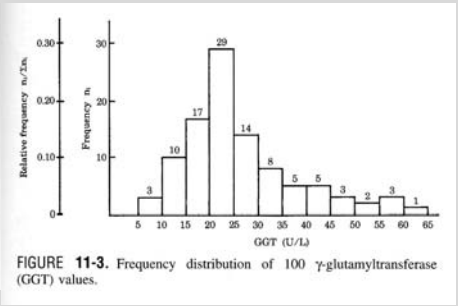

FIGURE 11-3. Frequency distribution of 100 γ-glutamyltransferase (GGT) values.

From: Kringle & Bogovich in Tietz Textbook of Clinical Chemistry 3rd Edn.

Real Data: non-Gaussian distributions

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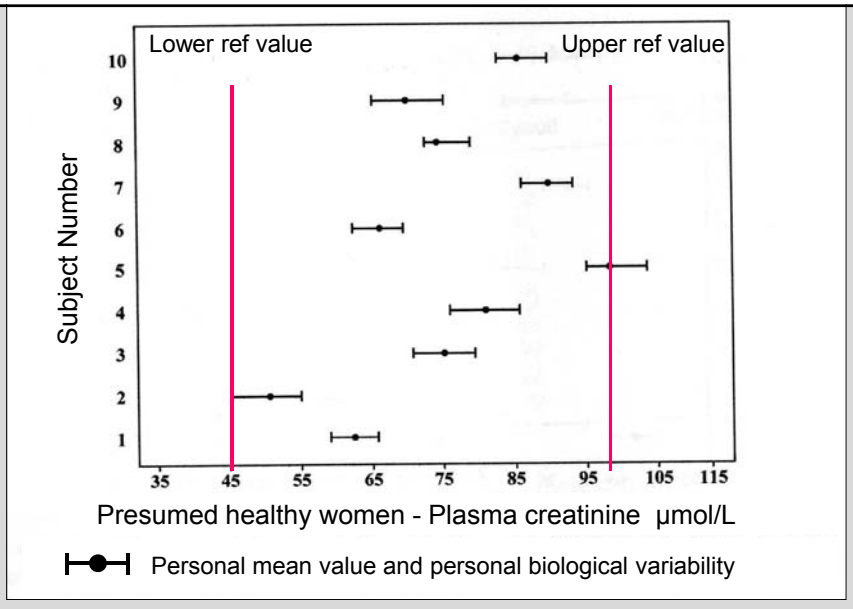

Reference interval insensitive to abnormality in the individual

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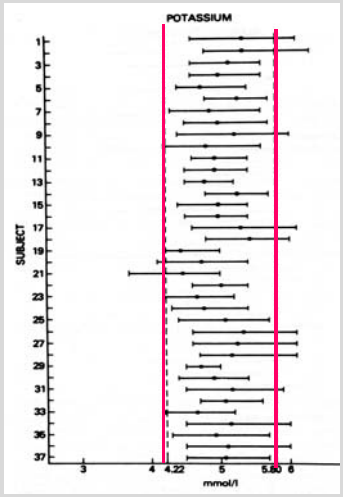
Fraser CG. Biological variation, 2001, AACC Press



Personal means similar

Personal biological variation similar

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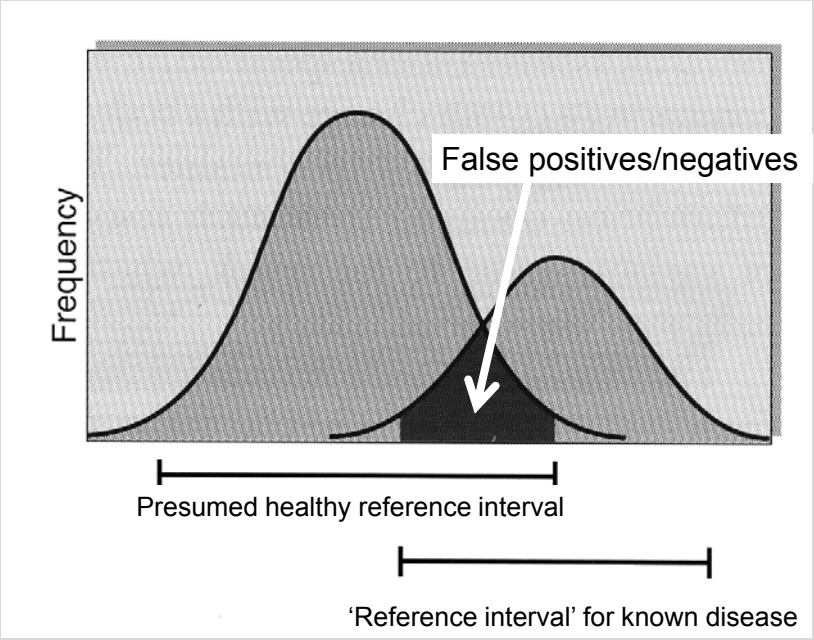
Fraser CG. Biological variation, 2001, AACC Press



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Modified from Gaw A et al. Clinical Biochemistry, Churchill Livingstone. 2003.

Reference intervals generally a ‘rough’ guide to whether a patient result is normal/abnormal

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Patient monitoring: Comparing serial results

Date:		14/10/13	31/03/14	17/10/14	06/05/15
Request Number:		37486439	39603081	40656269	42582596
HbA1c	(mmol/mol)	45	42	49	61
HbA1c	(%)	6.3	6.0	6.6	7.7
				Method	BIO-RAD Varia

Need to know imprecision over long time for same MP

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Patient monitoring: Comparing serial results

Smallest quantitative change that must be reliably measured?

Need analytical goals (target uncertainties)

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Quality hierarchy for setting analytical goals

Clinical outcomes

Proportion of within-individual biological variation

Clinical opinion

International expert bodies

State of the art/EQA performance

Target measurement uncertainties can be set

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IDEAL Approach to Estimating MU

For each MP in a laboratory :

- Define the measurand
- No modelling – use measured values to estimate MU
- Uncertainty of value assigned to end-user calibrator u_{cal}
- Uncertainty of significant bias correction u_{bias}
- Precision under intermediate conditions of reproducibility u_{inter}

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Precision under intermediate conditions of reproducibility

<u>For same MP in same laboratory:</u>

Capture all unavoidable changes in measuring conditions

e.g. lot changes of reagents, calibrators
different operators
re-calibrations
instrument maintenance

Will include e.g: electro-mechanical/temp fluctuations
automatic value rounding
environmental changes etc.

Use quality control (QC) data

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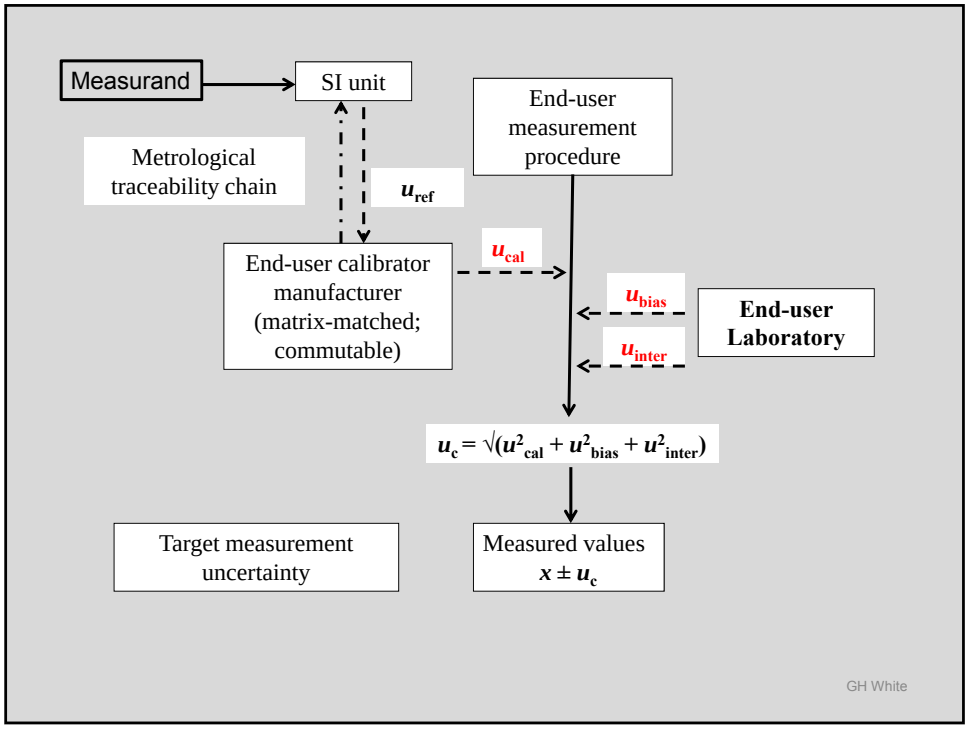
Measurand
SI unit
End-user measurement procedure
Metrological traceability chain
u_{ref}
End-user calibrator manufacturer (matrix-matched; commutable)
u_{cal}
u_{bias}
u_{inter}
End-user Laboratory
$u_c = \sqrt{(u^2_{cal} + u^2_{bias} + u^2_{inter})}$
Target measurement uncertainty
Measured values $x \pm u_c$
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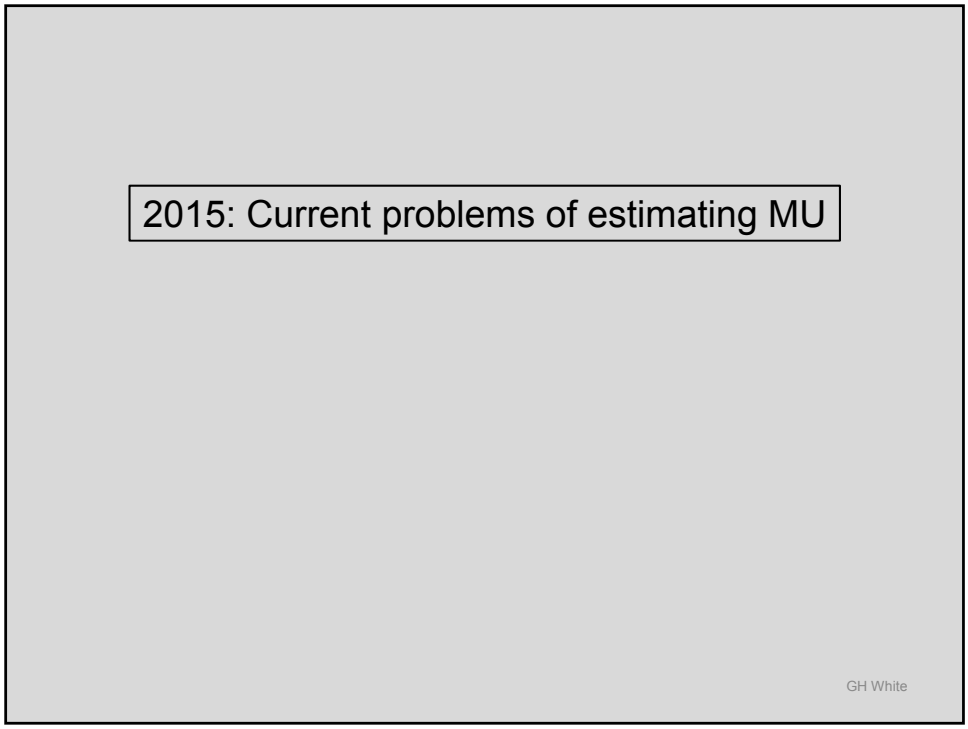
2015: Current problems of estimating MU
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Defining the measurand

Physico-chemically well-defined analytes:

e.g. Na, K, Mg, D-glucose, cholesterol

Allows:

Primary reference materials

Reference measurement procedures

Result traceability to mole if calibrator commutable

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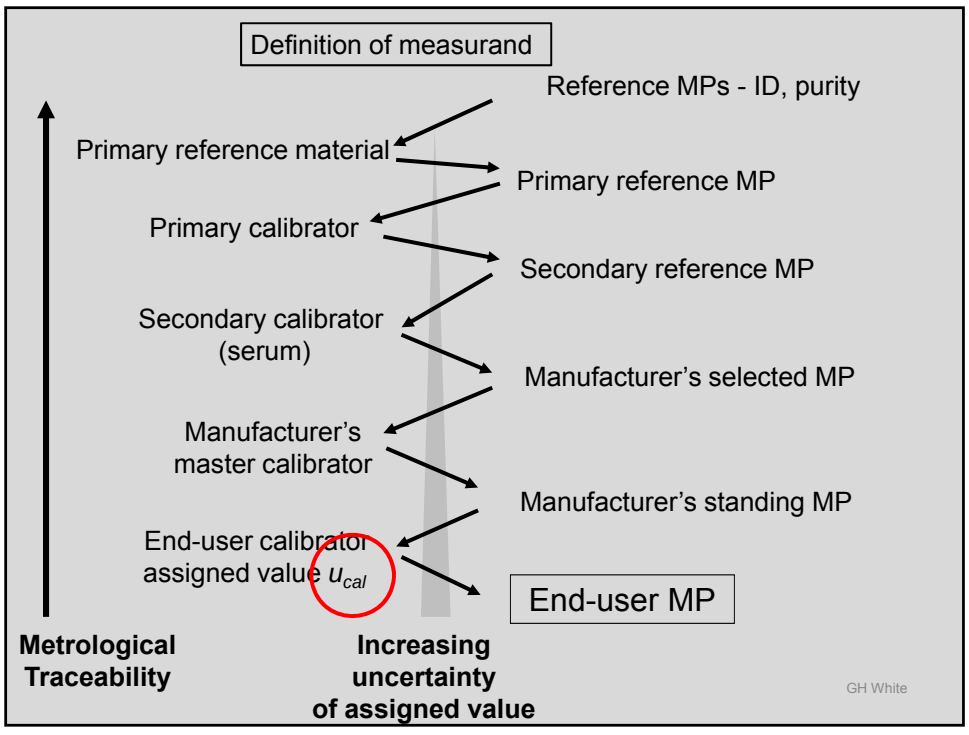

Defining the measurand

Poorly defined analytes e.g. Glycoprotein, steroid hormones

Multiple similar structures of ‘same’ hormone

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Variable number

side-chains on primary structure

Variable isoform proportions
in individuals

Variable isoform recognition by

different commercial MPs

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Different methods use antibodies against different epitopes

WHO Reference material
'FSH' isoforms

Different antibodies

'FSH' method manufacturers

Different FSH forms measured to different extents

Results from different FSH methods not equivalent

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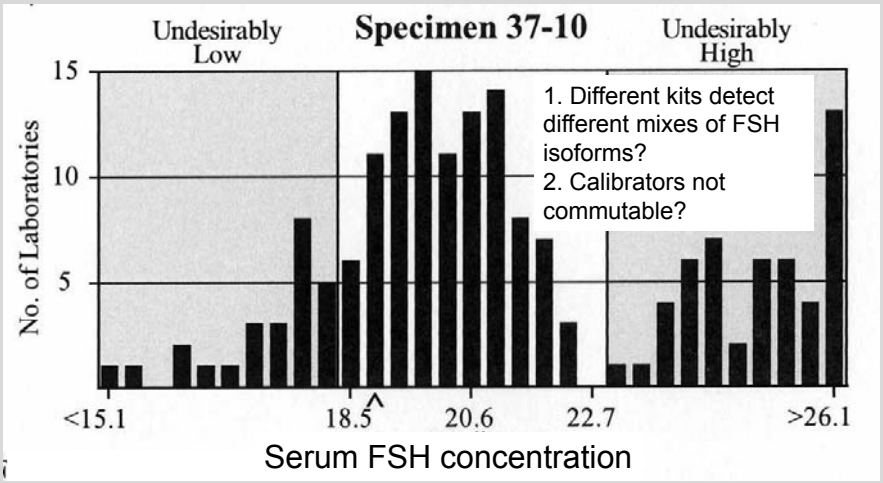
FSH: EQA results from all Australasian Laboratories

All labs measuring samples of same human serum



Common clinical decision value: Menopause: FSH >20 mIU/L!

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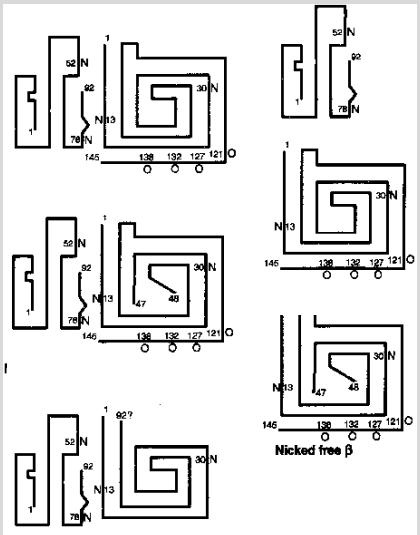
Intact hCG (αβ)

Nicked hCG

βhCG minus βCTP



Major serum hCG variants

Free α

Free β

Nicked free β

β-core

Urine

Serum 'hCG': Early pregnancy detection, threatened pregnancy, testicular cancer

Cole LA. 2002;

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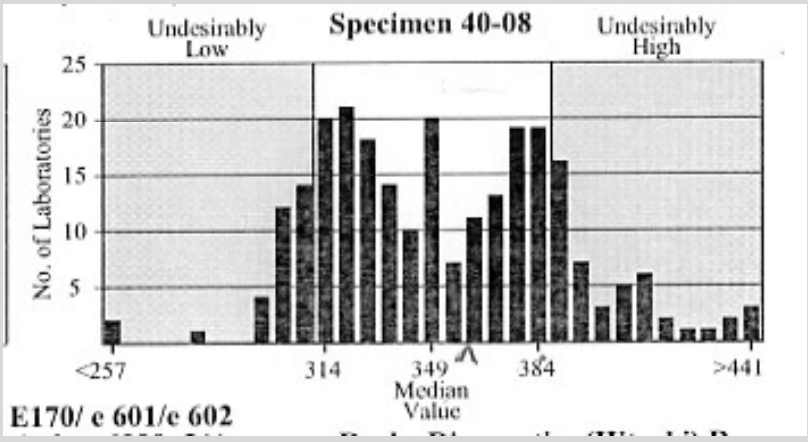
hCG: EQA results from all Australasian Laboratories



1. Different kits detect different mixes of hCG variants?
2. Calibrators not commutable?

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Ill-defined measurands suffer from:

No SI-traceable reference materials

No reference measurement procedures

and

Inadequate analytical selectivity

But are clinically valuable

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End-user calibrators

Hierarchy of Traceability

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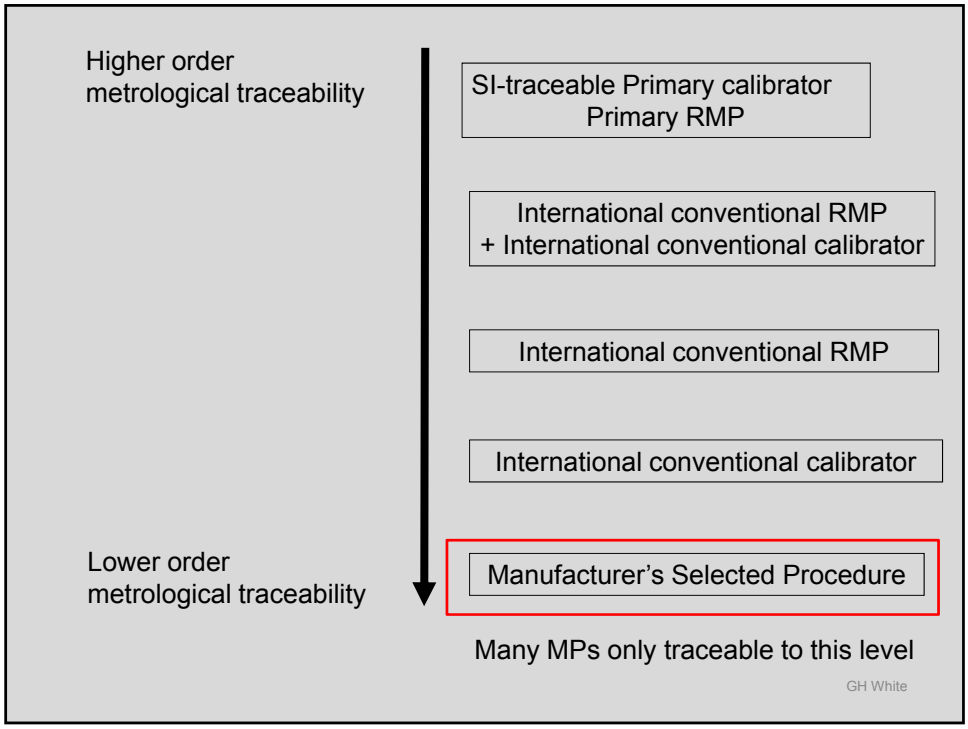

Summary

Many analytes:

- Inadequate definition of the measurand
- No high order reference materials
- No reference measurement procedures
- Use arbitrary measurement units (IU/L)
- WHO reference materials – no MU statement
- None, or incomplete u_{cal} from calibrator manufacturer

u_{cal} – lacking or incomplete

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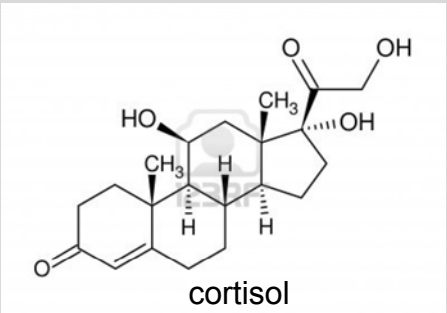
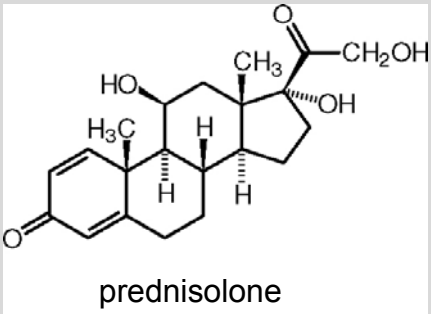
Routine measurement procedures often lack analytical selectivity



cortisol



prednisolone

Commonly used drug

30-70 % cross-reactivity in immunoassays for cortisol

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Uncertainty of bias correction u_{bias}

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Reference for bias assessment depends on measurand

- Secondary reference material or reference patient panel
- Trueness controls
- Target value for EQA peer group
- Inter-laboratory comparison

Bias and u_{bias} often not obtainable

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Summary so far

? Adequate definition of measurand

? ?

$$u_c = \sqrt{(u^2_{cal} + u^2_{bias} + u^2_{inter})}$$

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Precision: intermediate conditions of reproducibility

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Labs use Quality Control materials (QC)

Generally matrix-matched (human serum, plasma)

2-3 measurand concentrations across measuring interval

1-2 year supply

Measured when patient samples measured

Primary purpose: Assess MP performing to specification

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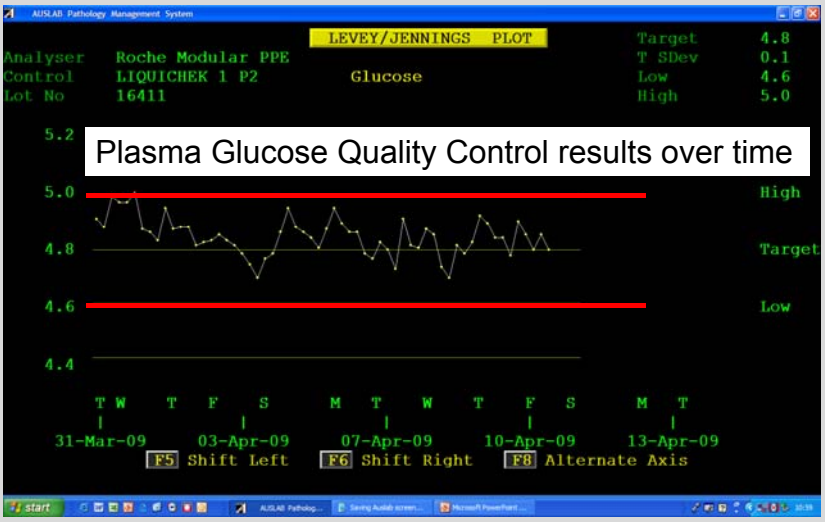

Mean ± 2SD: 4.8 ± 0.2 mmol/L

Visualisation of MU for glucose measurement by single MP

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Use QC values to estimate MU of patient values

Validation

For similar measurand concentration:

Compare SDs of QC and panel of typical patient samples

Assume long-term QC imprecision data valid to estimate MU

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? ? ?

Adequate definition of measurand

$$u_c = \sqrt{(u^2_{cal} + u^2_{bias} + u^2_{inter})}$$

u^2_{cal} , u^2_{bias} generally not significant relative to u_{inter}

For most measurands: estimated MU limited to imprecision

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Reporting patient results

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SA PATHOLOGY

FLINDERS MEDICAL CENTRE
FLINDERS DRIVE

U.R. **FMC - 01010630**

DOB: **21/03/63** 52 Years Sex: **M**

Lab Ref: **15-44208945** MCH

Page 1 of 1

BIOCHEMISTRY

			18/03/15	22/03/15	10/04/15	11/04/15	12/04/15	13/04/15	14/04/15
Time:			16:40	15:25	16:17	14:20	12:55	10:45	06:15
Lab No:			40788383	43177231	43175101	43174963	44652003	43175180	44208945
Type:			SERUM	SERUM	SERUM	SERUM	PLASMA	SERUM	PLASMA
Sodium	(137-145)	mmol/L	**135**	**132**	**127**	**128**	**133**	**136**	137
Potassium	(3.5-4.9)	mmol/L	3.9	3.7	4.5	3.7	3.9	4.3	3.9
Chloride	(100-109)	mmol/L	101	**99**	**95**	**93**	101	101	103
Bicarb.	(22-32)	mmol/L	26	27	28	29	23	27	24
Anion Gap	(7-17)	mmol/L	12	10	8	10	13	12	14
Glucose		mmol/L	4.9	**5.6**	4.7			**5.6**	
Urea	(2.7-8.0)	mmol/L	3.9	**2.5**	2.7	**2.4**	**1.8**	**1.8**	**2.3**
Creatinine	(50-120)	umol/L	83	87	61	69	68	74	72
eGFR		mL/min/1.73m2	> 90	88	> 90	> 90	> 90	> 90	> 90
calc.Osmo									
Urate		mmol/L	0.31						
Phosphate		mmol/L	1.16	1.01	1.26			1.26	
Tot. Ca		mmol/L	2.31	2.36	2.28			2.43	
calc.ICa			1.19	1.24	1.21			1.25	
Albumin		g/L	42	40	38	37	37	42	
Glob.			25	27	27	28	29	25	
Protein		g/L	67	67	65	65	66	67	
Tot. Bili		umol/L	9	9	8	8	3	7	
Con. Bili		umol/L							
GGT		U/L	**93**	**96**	**69**	**70**	**61**	**68**	
ALP		U/L	82	87	71	69	61	63	
ALT									
AST									
LD									
CK									
Mg									
Am									
Lip									

Results assumed to be best estimates

No MU reported – available from lab

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How do clinicians use quantitative laboratory results?

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Single test result rarely 'stand-alone' evidence

Panels of related tests Pattern of results over time

Results of related static/dynamic tests

Clinical history Clinical signs/symptoms

Imaging

Other diagnostic information

CLINICAL EXPERIENCE

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Example of biochemical diagnosis - glucose

Mr C - Clinical signs/symptoms ⟶ High blood glucose?

WHO Guidelines:

Random plasma glucose: ≥11.1 mmol/L

or

Fasting plasma glucose: ≥7.0 mmol/L

Plasma glucose: *U* = 0.2 mmol/L; 95 % confidence

Within-individual biological variation (CV): ~5 5 %

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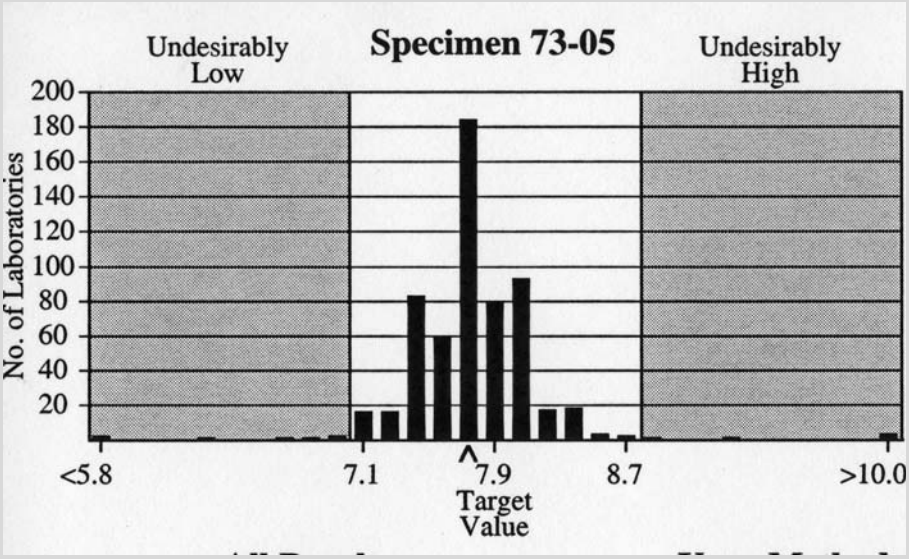
EQA: Plasma glucose (SI traceable, primary RMP & RM)



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Example of improving result interpretation

Prostate specific antigen (PSA): If > 4.0 ug/L – biopsy?

GP:
My patient has a serum PSA of 4.2 ug/L – is it definitely high?

The PSA has gone from 3.6 to 3.9 over 5 months – significant?

u_{rel} 2 %

Within-individual biological variation (CV): ~18 %

N.B. Personal biological variability >> relative standard MU

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CONCLUSIONS

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Advantages of using MU

- Overcomes limitations of total error approach, and simpler
- Set target uncertainties based on clinical requirements
- Quantitative evidence of meeting required clinical quality
- Improve interpretative advice to clinicians

Essential quality tool for medical laboratories

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Problems of standardisation, harmonisation, traceability of patients measured values

International Federation of Clinical Chemistry

Joint Committee for Traceability in Laboratory Medicine

American Association of Clinical Chemistry

European Federation of Laboratory Medicine

+

revision of ISO Standards

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<u>International aspirations:</u>

Patients' results to be metrologically traceable to highest available references

Results for any given measurand to be equivalent regardless of the laboratory and measurement procedure used

MU use by medical labs and In-Vitro Diagnostic Manufacturers will increase in the future

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