Gloucestershire Hospitals NHS
NHS Foundation Trust

Measurement Uncertainty

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06/02/15

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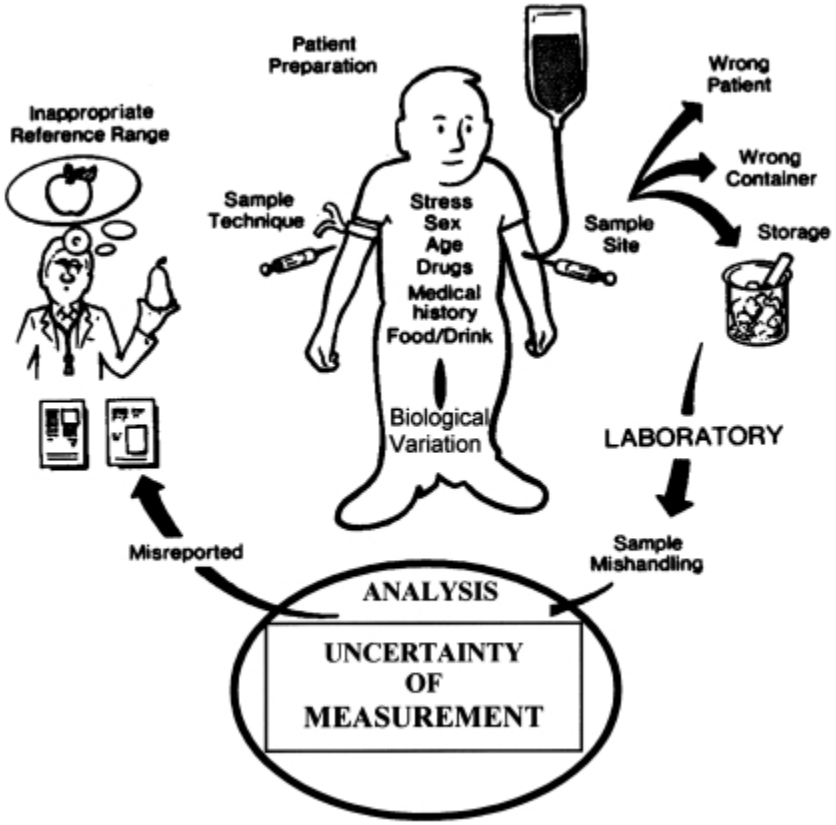
What is measurement uncertainty?

UKAS: “MU is a parameter, associated with the result of a measurement… that defines the range of the values that could reasonably be attributed to the measured quantity.”

What causes MU?



Why bother?

- The International Standard defines the specific requirements for competence and quality that a medical laboratory should meet in order to produce technically valid results.
- Previously: “the laboratory should determine the uncertainty of results, where relevant and possible.”

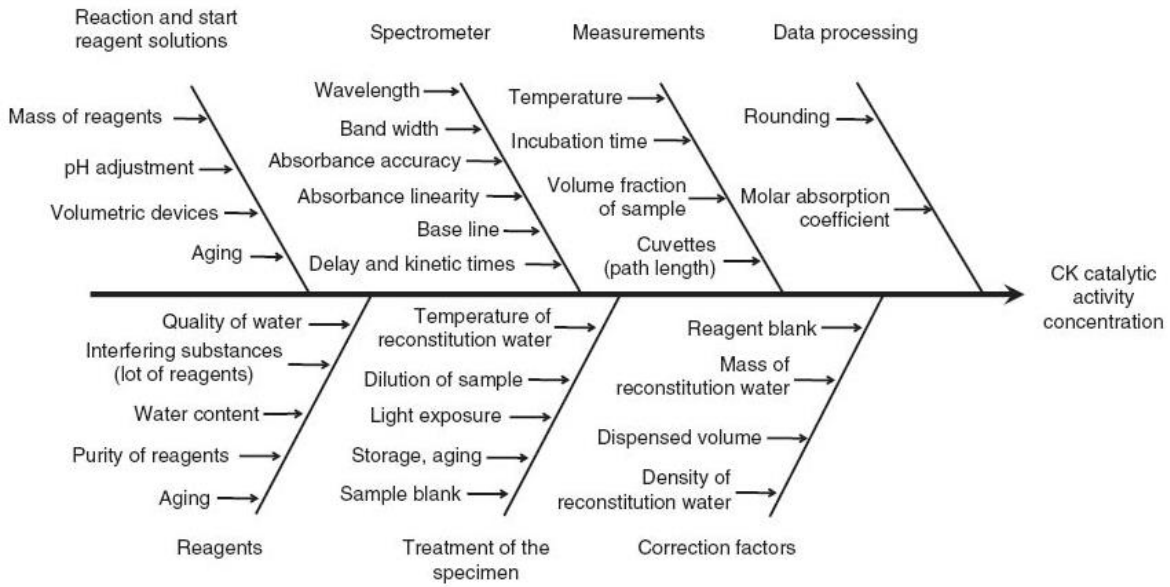
Why bother?

ISO 15189:2012:

“The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phases used to report measured quantity values on patients’ samples. The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.”

How to calculate MU

Type A (bottom-up) – complex mathematical model



Type B (top-down) – IQC under intermediate precision conditions

How to calculate MU

ISO 15189 gives some guidance.

1. The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value.
2. Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g., changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.

How to calculate MU

- MU = long term CV%
- Expressed as ±1.96 CV% (95% confidence limit)

How to calculate MU: example

Creatinine

- Biochem: four analysers over both sites.
- Measured six months' IQC:

Low QC	CV%	High QC	CV%
GRH Line 1	2.4	GRH Line 1	2.0
GRH Line 2	2.4	GRH Line 2	1.8
CGH 6000	3.2	CGH 6000	1.8
CGH 311	3.1	CGH 311	1.9
Average	**2.8**	**Average**	**1.8**

- Average overall = 2.3%
- Reported MU (± 1.96 CV%) = 4.5%
- e.g. creatinine result of 64 µmol/L could actually be anything between 60 and 67 µmol/L.

How does MU benefit patients?

Reference change values (RCVs)

- Determines whether the difference between two results is negligible due to uncertainty or significant due to a genuine change in the condition of the patient.

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Reference change values (RCVs)

- Determines whether the difference between two results is negligible due to uncertainty or significant due to a genuine change in the condition of the patient.
- Uses analytical variation (CV_A), aka MU, and biological variation (CV_I) data. Biological variation database available at: http://www.westgard.com/biodatabase1.htm

	Analyte	Number of papers	Biological Variation		Desirable specification		
			CVw	CVg	I(%)	B(%)	TE (%)
S-	Albumin	24	3.2	4.75	1.6	1.43	4.07
U-	Albumin, concentration, first morning	3	36.0	55.0	18.0	16.4	46.1
U-	Albumin, output, night urine	3	29.5	58.0	14.8	16.3	40.6
S-	Albumin, glycated	1	5.2	10.3	2.6	2.9	7.2
S-	Aldosterone	2	29.4	40.1	14.7	12.4	36.7
U-	Aldosterone	1	39.4	40.1	19.7	14.05	46.56
S-	Alkaline phosphatase	22	6.45	26.1	3.23	6.72	12.04

How does MU benefit patients?

Reference change values (RCVs)

- Analytical variation (CV_A), aka MU, and biological variation (CV_I) allow the laboratory to state (with 95% confidence) whether a result produced on a patient differs significantly from a previous result from a sample on that same patient.

$$RCV = 2.77 \times \sqrt{(CV_A^2 + CV_I^2)}$$

How does MU benefit patients?

Reference change values (RCVs)

Creatinine:

	QC1	QC3
Biological variation	6.0	6.0
Analytical variation (MU)	2.8	1.8
RCV = 2.77 x √(CV_A^2 + CV_I^2)	18.2	17.3
Average	17.7	

If a patient had a result of 64 µmol/L, the second result would have to be at least 75 µmol/L for there to be 95% confidence that it was both analytically and biologically different.

What next?

- ISO 15189: “upon request, the laboratory should make its estimates of measurement uncertainty available to laboratory users.”

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- Pathology web pages.

Creatinine

Assay	Creatinine
Key Words	CRT, U+E, eGFR
Specimen Collection	Serum (brown), Plasma (orange)
Turnaround time	8hrs
Test indications	Used in the assessment of renal function, as a marker of glomerular filtration rate
Interferences	Icterus (bilirubin) and some drugs may cause interference (see below for information on the use of enzymatic creatinine measurement). Variations in normal creatinine concentrations caused by ethnicity, age and gender may make eGFR unreliable.
Reference Range	<13 years: 15-70 umol/L >13 years: 50-120 umol/L Pregnant: 30-70 umol/L
Analytical error	3.8% (Enzymatic creatinine 2.7%)
Reference change value	19.7% (Enzymatic creatinine 18.2%)
	Enzymatic creatinine is an alternative method for measuring creatinine which is more specific to the creatinine analyte. It is used in patients under 18 years old and in

http://www.pch-pathlab.com/cms/?q=node/10

Uncertainty of measurement

Medical testing gives results that are subject to a degree of variability. This can be due to factors such as poor specimen collection, delays in transport, clerical and reporting errors. It is important to identify and minimise these factors.

Analytical error

The laboratory regularly assays quality control materials (IQC) in order to ensure the performance of our assays on a day-to-day basis. The variability of IQC results over time allows us to quantify the Analytical Error (AE) of an assay - that is to say the range of acceptable results at particular, clinically relevant, assay levels.
Each assay is also compared to the results from other national and international laboratories, this demonstrates any bias that our method shows against other methods (including a ‘reference method’) in the error calculation.
AE is expressed as a percentage. Thus we can be sure (with 95% certainty) that any result is within +/-1.96 x result x AE (%).
Consider that vital test - the serum rhubarb. Assuming a ‘true’ value of 10 with an AE of 5%:
Result = 10 ± 1.96 x 10 x 5 / 100
=> 10 ± 0.98
I.e. for a serum rhubarb of ‘10’ any result between 9.02 and 10.98 is analytically correct.

Reference change values

Reference change values (RCV) are useful in serial monitoring of patients. Changes in a patient’s results may be due to any of the following factors:

- Pre-analytical variation (e.g. specimen collection and storage)
- Analytical variation (AE as described above)
- Within-subject biological variation
- Variation due to pathological changes

The laboratory uses written procedures and protocols to limit the pre-analytical variation, and this is not normally included in

What next?

- ISO 15189: “upon request, the laboratory should make its estimates of measurement uncertainty available to laboratory users.”
- Pathology web pages.
- Regularly review.

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- Pathology web pages.
- Regularly review.
- Delta checks?

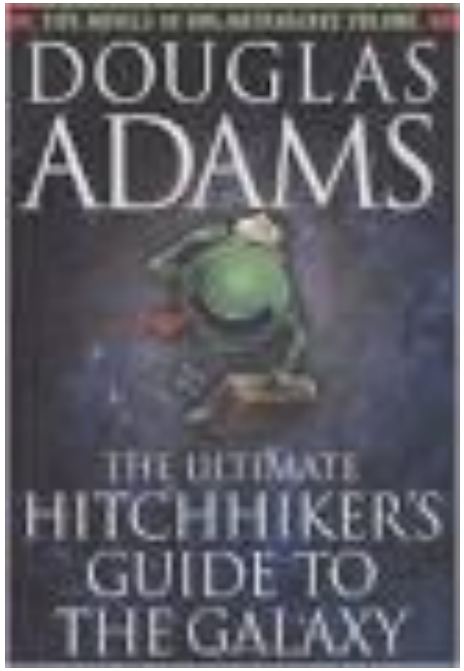
Conclusions

- Measurement uncertainty is here to stay and we will be being assessed on our adherence to ISO 15189.
- It is useful for both the laboratory in assessing quality and to the clinician who is establishing whether the patient's condition has changed.
- This all benefits the patient!

References

- ISO 15189:2012 Medical laboratories - requirements for quality and competence.
- Desirable Biological Variation Database specifications http://www.westgard.com/biodatabase1.htm
- White, G.H., Farrance, I. and AACB Uncertainty of Measurement Working Group (2004) Uncertainty of measurement in quantitative medical testing - a laboratory implementation guide. Clin Biochem Rev. 25(4), S1–S24. United Kindom Accreditation Service (UKAS) http://www.ukas.com/Technical-Information/Publications-and-Tech-Articles/Technical/technical-uncertain.asp
- What's New? Labs must MU. Westgard: http://www.westgard.com/labs-must-mu.htm
- Peterborough & Stamford Hospitals Pathology website http://www.pch-pathlab.com/cms/

Thank you!



"We demand rigidly defined areas of doubt and uncertainty!"

Douglas Adams, *The Hitchhiker's Guide to the Galaxy*