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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

14th International Scientific Meeting

Implementation of metrological traceability in laboratory medicine: where we are and what is missing

The irreplaceable contribution of measurement uncertainty to the standardization process

Sara Pasqualetti

For the Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Measurement Uncertainty (MU) definition

Parameter characterizing the dispersion of the quantity values being attributed to a measurand

[International Vocabulary of Metrology Basic and general concepts and associated terms (VIM). 3rd ed. 2012]

In lay terms, MU represents the interval of possible values for a measurand for which a result was obtained.

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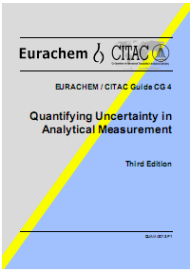
"…In general use, the term 'uncertainty' relates to the concept of doubt… [however] uncertainty of measurement does not imply doubt about the validity of a measurement; on the contrary, *knowledge of the measurement uncertainty implies increased confidence in the validity of a measurement result…*"

[Ellison SLR, Williams A, eds. (2012). Eurachem Guide: Quantifying Uncertainty in Analytical Measurement, Eurachem, 3rd ed.]



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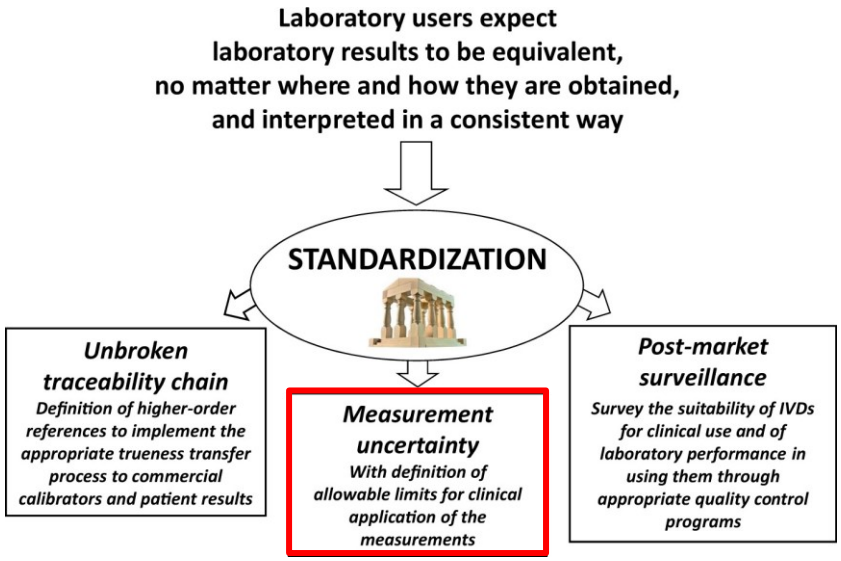
If I estimate my ***uncertainty*** *of measurement it is no longer an uncertainty:* ***it is now the probability limit within which the result will fall***

Why do we need MU?

MU contributes in producing standardized laboratory results



Panteghini M et al. Clin Chem, Volume 67, Issue 12, December 2021, Pages 1590–1605

ISO 15189:2012 AND MEDICAL LABORATORIES ACCREDITATION

introduced the estimation of measurement uncertainty as a specific requirement for the accreditation of medical laboratories

5.5.1.4 "…(medical laboratories)… shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples."

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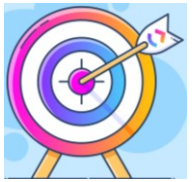
How to deal with Measurement Uncertainty

Measurement Uncertainty

MU Estimation

Definition of Analytical Performance Specification for MU

Verification that MU fulfills defined APS



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How to calculate MU in medical laboratories

"Top-down" approach

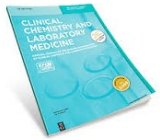
It estimates MU of laboratory results by *using internal quality control data* to derive the random components of uncertainty and commercial calibrator information.

Practical approach to estimation of MU of quantities produced by measurement procedures intended to measure biological measurands, *to be applied in medical laboratory*

ISO/TS 20914:2019
MEDICAL LABORATORIES -- PRACTICAL GUIDANCE FOR THE ESTIMATION OF MEASUREMENT UNCERTAINTY
First edition: July 2019

with the inspiring concept....
MU must be defined across the entire traceability chain

[Panteghini M, Clin Chem Lab Med 2012;50:1237]



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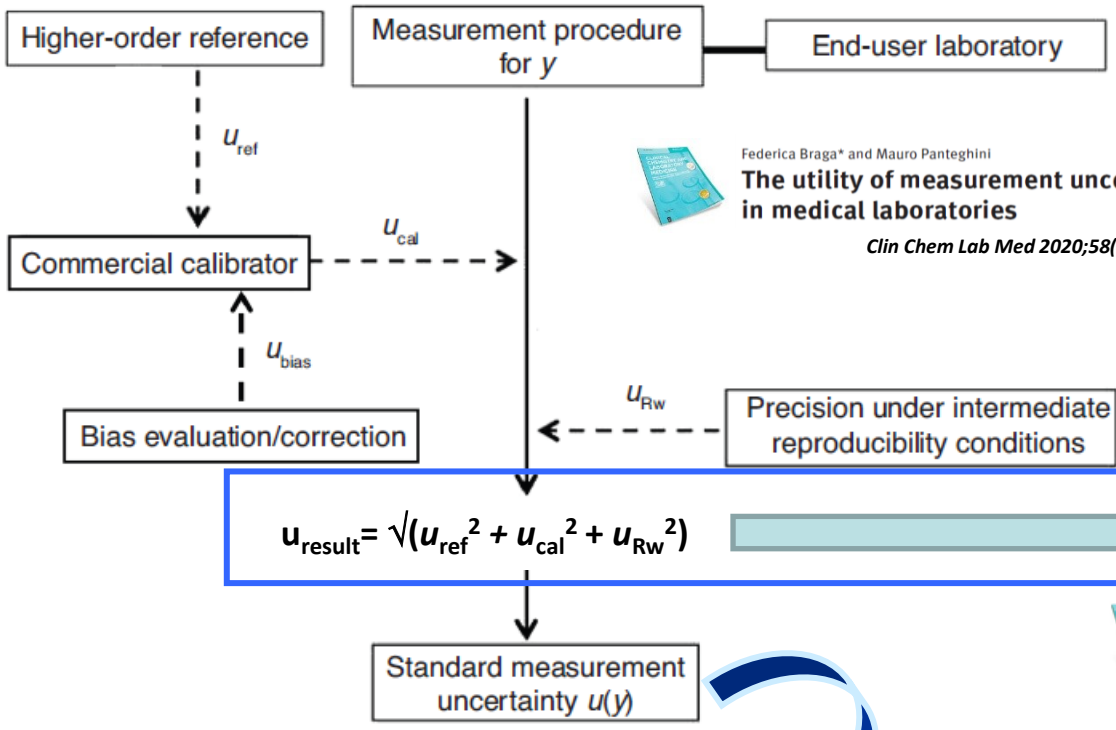
Sources of MU with the 'top-down' approach



Federica Braga* and Mauro Panteghini

The utility of measurement uncertainty in medical laboratories

Clin Chem Lab Med 2020;58(9):1407-13

Mauro Panteghini*

The simple reproducibility of a measurement result does not equal its overall measurement uncertainty

Clin Chem Lab Med 2020;60(10):e221-e222

Maximum allowable MU

The magnitude of MU should be suitable for a result to be used in a medical decision... For a given measuring system, estimating the uncertainty of the results produced is of very limited value unless it can be compared with the allowable MU based on the quality of results required for medical use.

ISO/TS 20914:2019
MEDICAL LABORATORIES -- PRACTICAL GUIDANCE FOR THE ESTIMATION OF MEASUREMENT UNCERTAINTY

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Standardization and target for allowable MU

DE GRUYTER Clin Chem Lab Med 2017; 55(2): 189–194

Opinion Paper

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

APS model 1: outcome-based → The measurand has a central role in diagnosis and monitoring a specific disease

APS model 2: biological variation → The measurand is under strict metabolic control

APS model 3: state-of-the-art → The measurand has neither central diagnostic role nor sufficient homeostatic control

The models *do not constitute a hierarchy*; some models are better suited for certain measurands. Attention should primarily direct toward the measurand and its biological and clinical characteristics.

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u_{result} must fulfill APS

Ospedale Luigi Sacco
AZIENDA OSPEDALIERA - POLO UNIVERSITARIO

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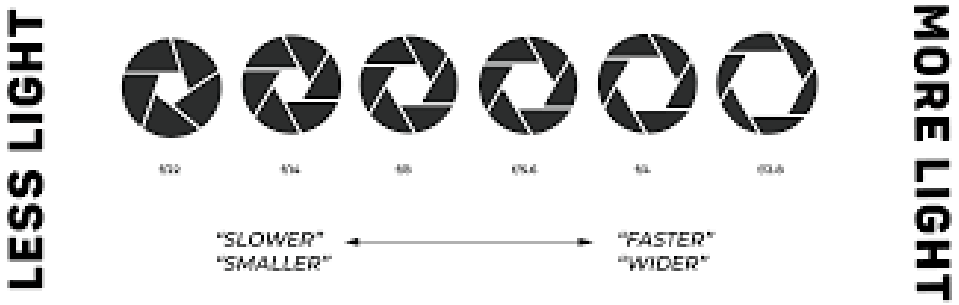
APERTURE



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A project for establishing **A**nalytical **Per**formance Specifica**t**ions for Meas**ure**ment Uncertainty of common measurands based on Milan models

APERTURE PROJECT

Step 1

- 40 measurands among the most requested tests in different analyte categories were selected

Step 2

- Allocation of each measurand to one of the Milan models based on its biological and clinical characteristics

Step 3

- Definition of APS for MU by reviewing available literature and selecting adequate information

Step 4

- Verification for each analyte that MU fulfills the defined APS

Step 1

APERTURE PROJECT

Measurand selection:
We identified 40 measurands among the most requested tests in different analyte categories

Urine albumin
Serum total cholesterol
Serum albumin
Serum HDL cholesterol
Serum triglycerides
Blood platelets
Serum alkaline phosphatase
Serum aspartate aminotransferase
Serum creatine kinase
Serum γ-glutamyltransferase
Serum lactate dehydrogenase
Serum pancreatic amylase
Serum total proteins
Serum immunoglobulin G
Serum immunoglobulin A
Serum immunoglobulin M
Serum prostate-specific antigen
Serum magnesium
Serum urate
Plasma homocysteine
Red blood cells
White blood cells
Serum digoxin

Plasma glucose
Blood HbA_{1c}
Blood total hemoglobin
Serum 25-Hydroxyvitamin D_3
Plasma sodium
Plasma potassium
Plasma chloride
Plasma total calcium
Plasma creatinine
Plasma urea
Plasma total bilirubin
Plasma alanine aminotransferase
Plasma C-reactive protein

TSH
Free T3
Free T4

Cardiac troponin

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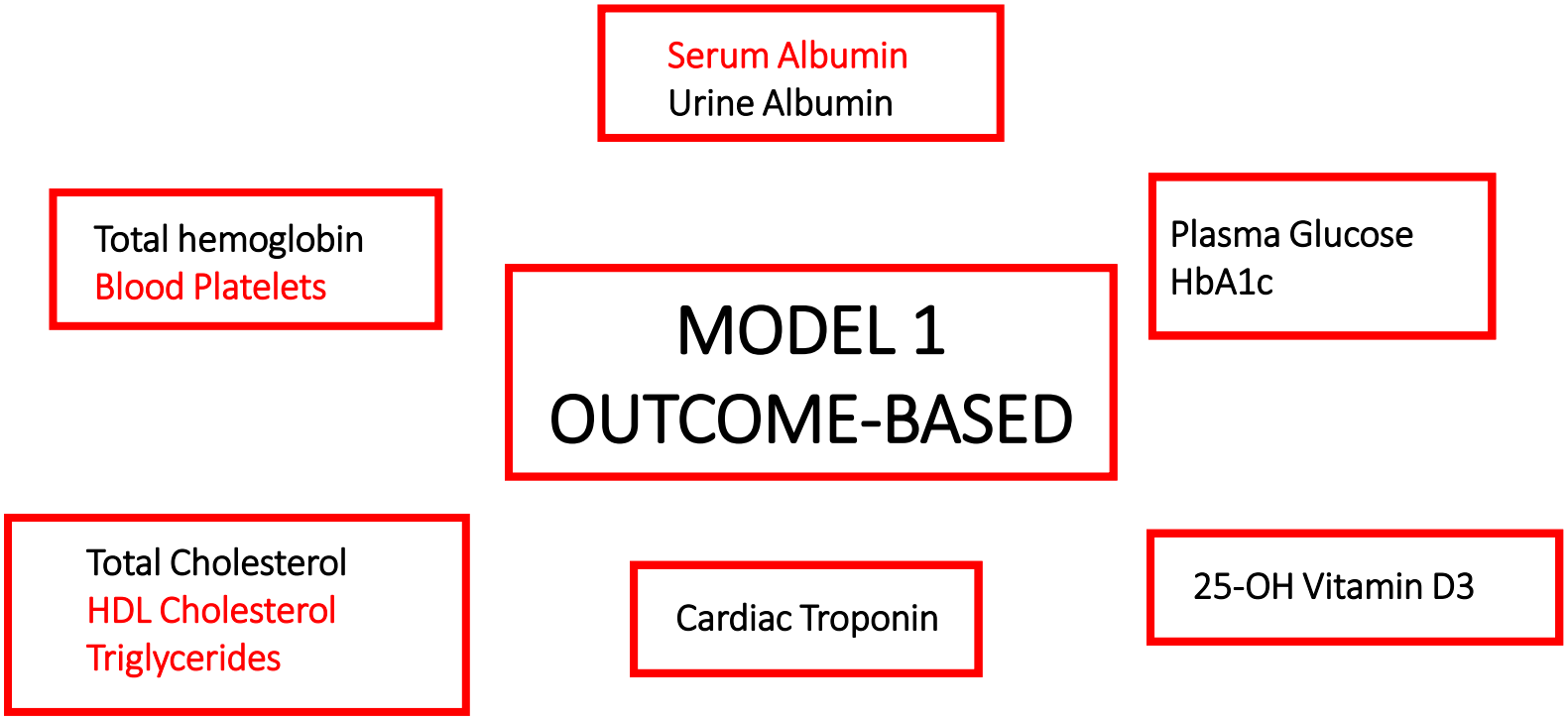
Step 2



For measurands belonging to the model 1, we searched peer-reviewed literature for outcome studies dealing with the main clinical use of the measurand and evaluating the impact of random analytical variability on clinical outcomes.
For measurands in red, no outcome-based data in literature were retrieved.
Therefore, considering their physiological homeostatic control, to derive APS we temporarily allocated those measurands to the biological variation model.

Step 2

Plasma Na, K & Cl
Plasma Ca & Mg

Serum Creatinine
Serun Urea
Serum Urate
Total & Conjugated Bilirubin
Plasma Homocysteine

MODEL 2 BIOLOGICAL VARIATION

ALT & AST
Creatine kinase (CK)
Alkaline phosphatase (ALP)
γ-glutamyltransferase (GGT)
Lactate dehydrogenase (LDH)
Pancreatic amylase
PSA

White Blood cells
Red Blood Cells

Temporarily allocated:
Serum Albumin
Blood Platelets
HDL Cholesterol
Triglycerides

Serum Total Protein
IgA, IgG, IgM
Free T3 & T4

For measurands belonging to the model 2, we retrieved BV publications in compliance to the 14 BV data critical appraisal checklist quality items (BIVAC-QI). From these publications, we derived CV_I estimates needed to calculate APS for MU.

Step 2

C-reactive protein

Thyroid stimulating hormone

MODEL 3
STATE OF THE ART

To obtain the highest level of achievable analytical performance for measurands belonging to the model 3, we compared average u_{resut} of widely used measuring systems and selected the best performance as APS for MU.

Digoxin

MODEL 1&2

Drugs need a specific approach when deriving APS, based on fundamental pharmacokinetic theory and average elimination half-life of the drug.
Although the concentration of drugs does not fluctuate randomly around a homeostatic set point, this approach has a relationship with biological knowledge. On the other hand, TDM is linked to the patient outcome in defining the levels of drug which are potentially toxic or when the treatment can be ineffective.
Accordingly, a hybrid model between the models 1 and 2 was proposed for drugs.

Step 3

APERTURE PROJECT

Federica Braga* and Mauro Panteghini

Clin Chem Lab Med 2021;59:1362

Performance specifications for measurement uncertainty of common biochemical measurands according to Milan models

Measurand	Milan model	APS for standard MU, %	
		Desirable	Minimum
Plasma glucose	Outcome-based	2.00	3.00[b]
Blood HbA_{1c}	Outcome-based	3.00	3.70
Blood total hemoglobin	Outcome-based	2.80	4.20[b]
Serum 25-Hydroxyvitamin D_3	Outcome-based	10.0	15.0
Plasma sodium	Biological variation[g]	0.27	0.40
Plasma potassium	Biological variation[g]	1.96	2.94
Plasma chloride	Biological variation[g]	0.49	0.74
Plasma total calcium	Biological variation[g]	0.91	1.36
Plasma creatinine	Biological variation[g]	2.20	3.30
Plasma urea	Biological variation[g]	7.05	10.6
Plasma total bilirubin	Biological variation[g]	10.5	15.7
Plasma alanine aminotransferase	Biological variation[g]	4.65	6.98
Plasma C-reactive protein	State of the art	3.76	5.64[b]

The Journal of APPLIED LABORATORY MEDICINE

AACC

Measurement uncertainty of thyroid function tests on Abbott Alinity i needs to be improved

Francesca Borrillo*, Sara Pasqualetti, Mauro Panteghini

Research Center for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

	Milan model	APS for u_{result}	
		Desirable	Minimum
TSH	State of the art	2.89%	4.34%
Free T3	Biological variation	2.35%	3.53%
Free T4	Biological variation	2.80%	4.20%

Clin Chem Lab Med. 2022 doi: 10.1515/cclm-2022-0806. OAP

Federica Braga, Sara Pasqualetti, Francesca Borrillo*, Alessia Capoferri, Mariia Chibireva, Leila Rovegno and Mauro Panteghini

Definition and application of performance specifications for measurement uncertainty of 23 common laboratory tests: linking theory to daily practice

Measurand	Milan model	APS for u_{result} (%)	
		Desirable	Minimum
Urine albumin	Outcome	9.00	17.0
Serum total cholesterol	Outcome	3.00	7.00
Serum albumin	2Temp[a]	1.25	1.88
Serum HDL cholesterol	2Temp	2.84	4.26
Serum triglycerides	2Temp	9.90	14.9
Blood platelets	2Temp	4.85	7.28
Serum alkaline phosphatase	Biological variation	2.65	3.98
Serum aspartate aminotransferase	Biological variation	4.75	7.13
Serum creatine kinase	Biological variation	7.25	10.9
Serum γ-glutamyltransferase	Biological variation	4.45	6.68
Serum lactate dehydrogenase	Biological variation	2.60	3.90
Serum pancreatic amylase	Biological variation	3.15	4.73
Serum total proteins	Biological variation	1.30	1.95
Serum immunoglobulin G	Biological variation	2.20	3.30
Serum immunoglobulin A	Biological variation	2.50	3.75
Serum immunoglobulin M	Biological variation	2.95	4.43
Serum prostate-specific antigen	Biological variation	3.40	5.10
Serum magnesium	Biological variation	1.44	2.16
Serum urate	Biological variation	4.16	6.24
Plasma homocysteine	Biological variation	3.52	5.27
Red blood cells	Biological variation	1.55	2.33
White blood cells	Biological variation	5.65	8.48
Serum digoxin	1&2[b]	6.00	9.00

Step 4

APERTURE PROJECT

....to link theory to daily practice

$$u_{result} = \sqrt{(u_{ref}^2 + u_{cal}^2 + u_{Rw}^2)}$$

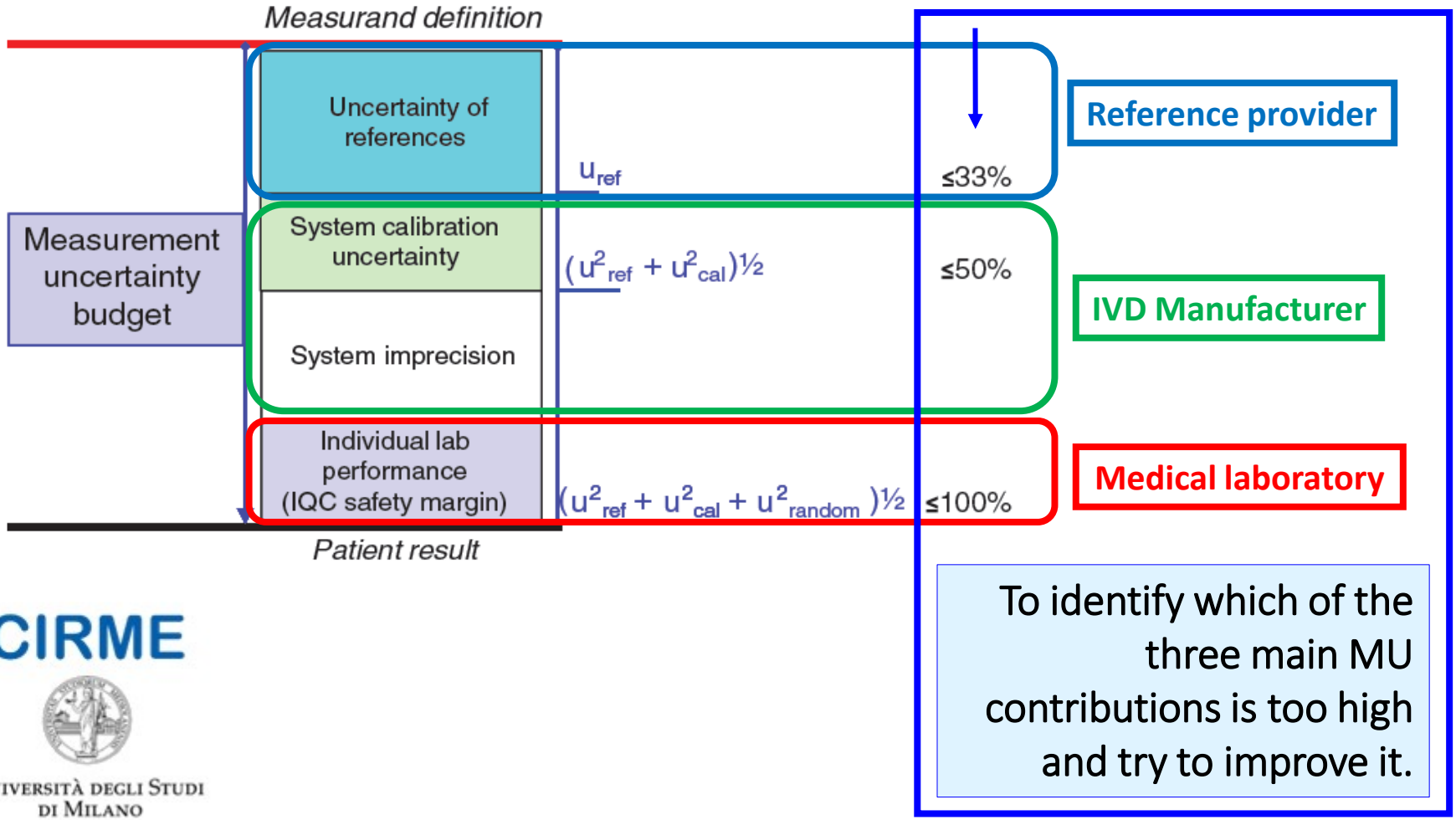
to estimate for considered tests the u_{result} and compare it with set forth APS to see if today's measuring systems can meet them.

Out of 40 evaluated measurands, the majority (26) achieved the desirable MU, eight fulfilled minimum APS, and six (i.e., plasma sodium and chloride, serum albumin, free thyroid hormones, and plasma homocysteine) exceeded the established goals.

How to deal when MU is out of APS

Recommended limits expressed as percentage of total MU budget goal

Braga et al., Clin Chem Lab Med. 2015;53(6):905-912
Braga F, Panteghini M. Clin Biochem 2018;57:7



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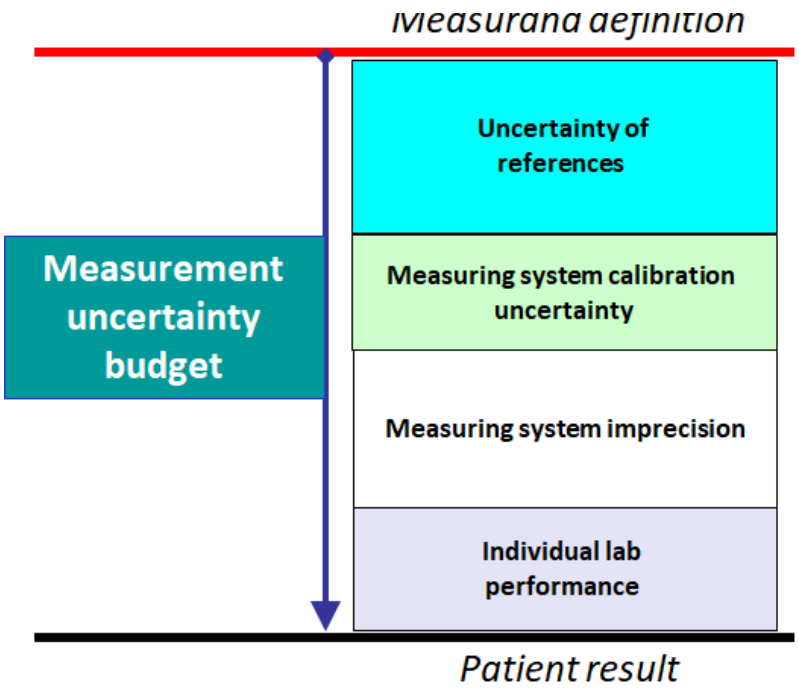
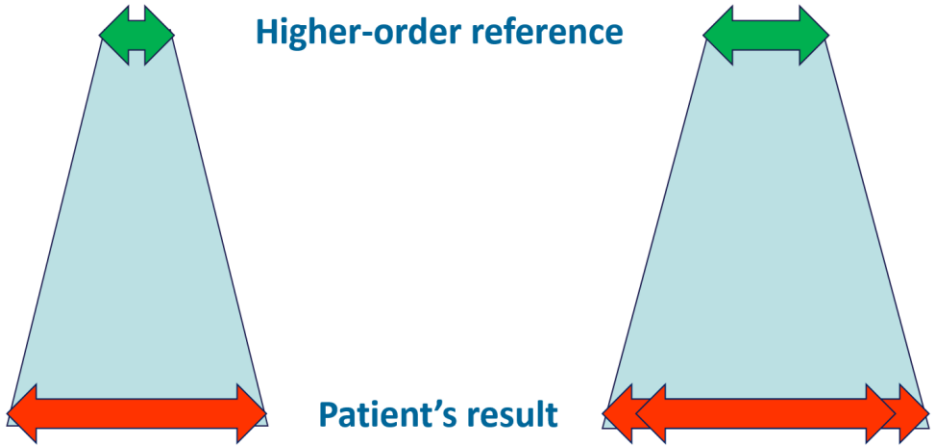
REFERENCE PROVIDER contribution to the MU budget (u_{ref})



Recommended limit 33%

Reference provider

Due to MU propagation in the calibration hierarchy, u_{ref} should be significantly lower than APS for MU of patient results



Adapted from G. Jones, 5th CIRME International Scientific Meeting – Milan, IT – Nov 2011

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EXAMPLE

Serum creatinine

Allowable limit for the standard MU of creatinine reference materials @ 33% of the goal

1.1% minimum

0.75% desirable

Creatinine uncertainty

3.3% minimum

2.2% desirable

Secondary RM/RMP	Traceability of assigned values	Nominal value, µmol/L	Combined standard uncertainty, %[a]
JRC BCR-573 (lyophilized human serum)	By ID/GC/MS and HPLC[b] calibrated with the NIST SRM 914a	68.7	*1.02*
JRC BCR-574 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	105.0	**0.62** ✅
JRC BCR-575 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	404.1	*0.88*
LGC ERM-DA250a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	358.0	5.87
LGC ERM-DA251a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	197.0	5.58
LGC ERM-DA252a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	27.5	15.6
LGC ERM-DA253a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	449.0	3.56
LNE CRM Bio 101a level 1 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	53.04	*1.09*
LNE CRM Bio 101a level 2 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	550.54	**0.56** ✅
CENAM DMR-263a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914a	66.4	2.18
ID/GC/MS	By calibration with high purity crystalline creatinine	151.9[c]	**0.49**[c] ✅
		352.9[c]	**0.50**[c] ✅
ID/LC/MS	By calibration with high purity crystalline creatinine	152.1[d]	*0.82*[d]
		350.5[d]	**0.40**[d] ✅
ID/SERS	By calibration with high purity crystalline creatinine	345.7[e]	1.23[e]
		492.0[e]	2.24[e]

IMPORTANT

When different options are available in making a choice, IVD manufacturers should consider the suitability of higher-order references in terms of MU by selecting ones with less impact on the total MU budget.

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JCTLM

Task Force on Reference Measurement System Implementation

Letter to the Editor

Clin Chem Lab Med 2020;59:e129-e132

Sara Pasqualetti*, Mariia Chibireva, Francesca Borrillo, Federica Braga and Mauro Panteghini

Improving measurement uncertainty of plasma electrolytes: a complex but not impossible task

Plasma Sodium

EXAMPLE

Alinity Na measuring system as currently marketed

Reference procedure — Flame emission spectrophotometry — u_{ref} 0.57%

ICT serum calibrator — u_{cal} 0.65%

Clinical samples — u_{result} 0.77% — MAU 0.41%

Plasma Na: 160 mmol/L

The uncertainty of this measuring system *does not fulfil* the maximum allowable uncertainty (MAU) according to analytical performance specifications.

Alinity Na measuring system if the selected higher-order RMP would be changed to ion chromatography

Reference procedure — Ion chromatography — u_{ref} 0.20%

ICT serum calibrator — u_{cal} 0.37%

Clinical samples — u_{result} 0.56% — MAU 0.41%

Plasma Na: 160 mmol/L

The uncertainty of this measuring system *is close to fulfil* the maximum allowable uncertainty (MAU) according to analytical performance specifications.

"By replacing flame emission spectrophotometry with ion chromatography in the Na value-assigning process of Abbott calibrators, u_{result} on Alinity measuring system could be improved from about 0.80% to 0.55%."

Letter to the Editor

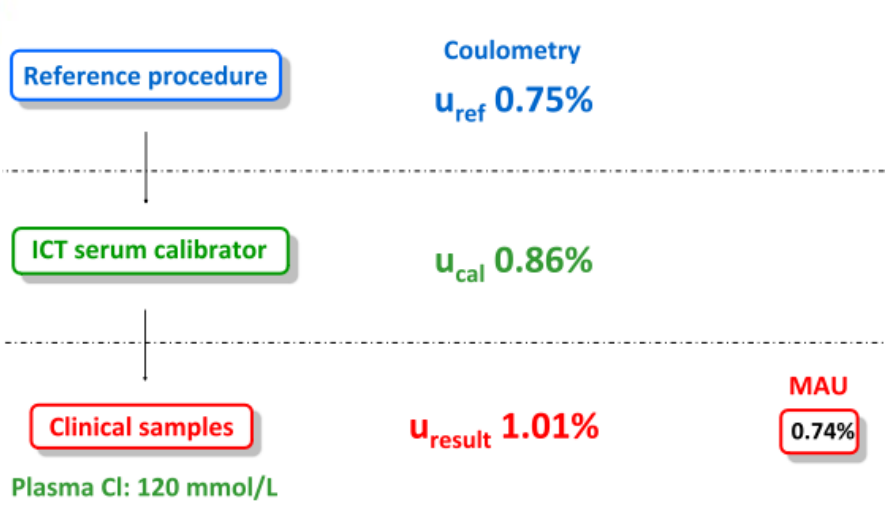
Clin Chem Lab Med 2020;59:e129-e132

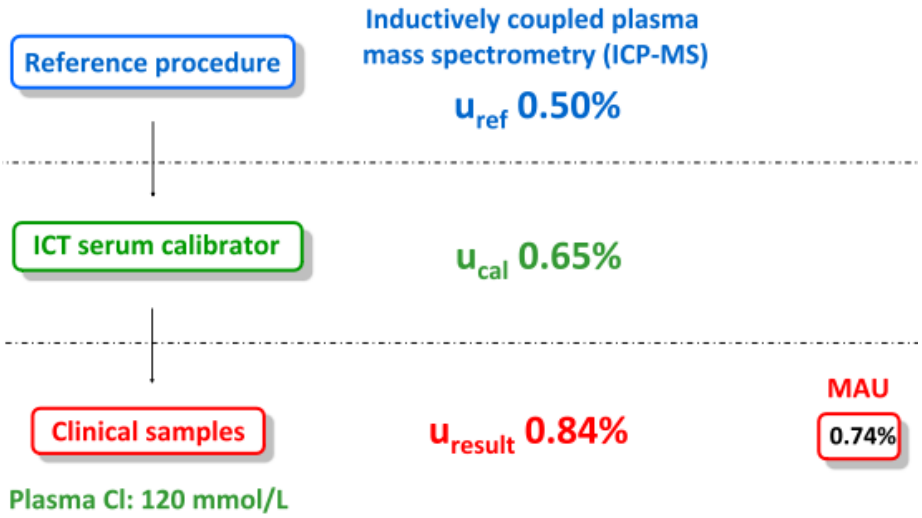
Sara Pasqualetti*, Mariia Chibireva, Francesca Borrillo, Federica Braga and Mauro Panteghini

Improving measurement uncertainty of plasma electrolytes: a complex but not impossible task

Plasma Chloride

EXAMPLE





The MU of the current IVD measuring systems has almost no possibility to fulfil APS for the total MU budget on clinical samples, regardless of the higher-order reference selected.

To this regard, it would be interesting to determine whether the use of a RMP based on the ion chromatography principle may improve the associated MU and permit the MU for chloride to get close to the APS as already observed for other plasma/serum ions.

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Pasqualetti S et al, Clin Chem Lab Med 2021;59:e129
Panteghini M et al, Clin Chem 2021;67:1590

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Task Force on Reference Measurement System Implementation

IVD manufacturers should not only direct their efforts on improving instrument performance but operate to reduce as much as possible u_{ref} (and consequently u_{cal}) especially when APS are stringent.

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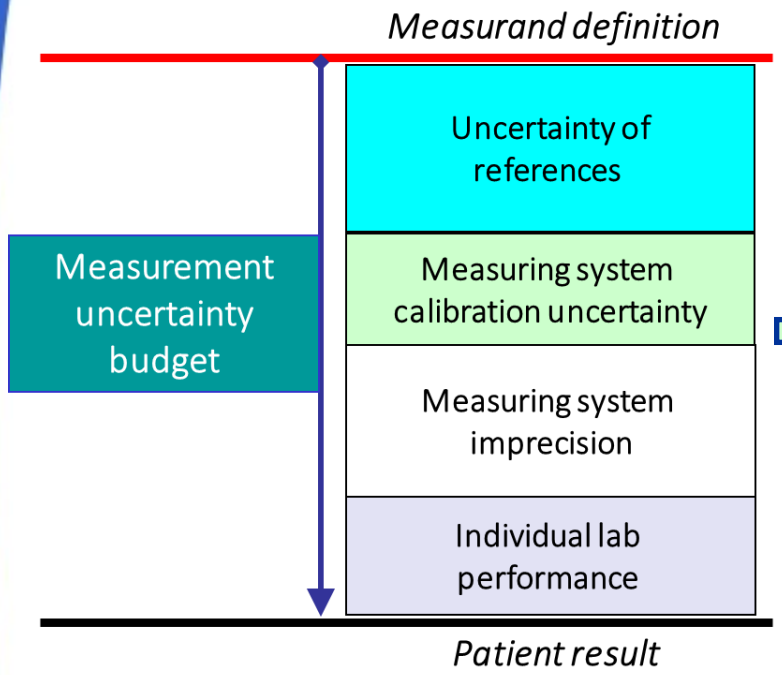
COMMERCIAL CALIBRATOR contribution to the MU budget (u_{cal})



- u_{cal} should represent a proportion of the MU budget allowed for clinical laboratory results (e.g., 50% of MU APS), in order to leave enough MU budget usable by individual laboratories to produce clinical results of acceptable quality
- if higher-order references do not exist, $u_{value\ ass}$ contributes to the overall uncertainty of measurement results.
- If calibrators are offered without MU, it is up to the laboratory professionals to ask manufacturers and obtain this information for the correct estimate of u_{result}

Manufacturers should estimate the combined uncertainty!d

Recommended limit 50%

$$u_{cal} = (u_{ref}^2 + u_{value\ ass}^2)^{½}$$

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EXAMPLE

Abbott Sigma Strong Project

Abbott GmbH & Co. KG
Max-Planck-Ring 2
65205 Wiesbaden
Germany

GGT1

- Biological Samples (Reference Commutable Material)
- IFCC traceable Calibrator Factor
- Routine samples

IFCC Primary Reference Procedures for the Measurement of Catalytic Activity Concentrations of Enzymes at 37°C

Manufacturer's standing measurement procedure

Gamma-Glutamyl Transferase

(GGT REF. 07P73)

Abbott Ireland
Diagnostics Division
Lisnamuck, Longford
Co. Longford
Ireland

GGT2

- ERM-AD452/IFCC
- Consolidated Chemistry Calibrator $_{ConCC}$ (REF 04V6201)
- Routine samples

IFCC Primary Reference Procedures for the Measurement of Catalytic Activity Concentrations of Enzymes at 37°C

Manufacturer's standing measurement procedure

Gamma-Glutamyl Transferase2

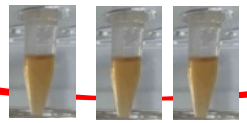
(GGT2 REF 04T96)

IFCC Standardized Calibration Factor

2.0%

$u_{result}=\sqrt{(u_{cal}^2 + u_{Rw}^2)}$

CIRME REFERENCE SAMPLES



Consolidated Chemistry Calibrator (ConCC)

9.1%

$u_{result}=\sqrt{(bias^2 + u_{bias}^2 + u_{cal}^2 + u_{Rw}^2)}$

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γ-Glutamyltranferase u_{result}

Bianchi G et al. CCLM 2022;60:e228

Letter to the Editor

Clin Chem Lab Med 2022; 60(10): e228–e231

Giorgia Bianchi*, Giulia Colombo, Sara Pasqualetti and Mauro Panteghini

Alignment of the new generation of Abbott Alinity γ-glutamyltransferase assay to the IFCC reference measurement system should be improved

Slope of 1.08 between the GGT2 and GGT1 assays reported in Abbott's IFU: what limit of acceptable bias Abbott uses for the GGT value-assignment of ConCC and for internal validation of the GGT kit and transfer of performance from different generation of assays?

→ Abbott use an accuracy specification of +/- 7 % to a recognized standard material i.e. ERM AD452/IFCC

Abbott accepts a regression slope of 0.86 to 1.14 (correlation coefficient ≥0.975) for samples between the GGT2 and GGT1 (~10%)

Abbott accepts a TE of 22% or +/- 8 U/L across the medical range of 76 U/L to 1140 U/L for serum/plasma (???)

Was the commutability of ERM-AD452/IFCC reference material used for directly calibrating the GGT2 assay assessed?

→ Manufacturer disregards commutability of ERM-AD452/IFCC reference material.

Why the manufacturer decided to replace the use of a calibration factor (stable in the daily use of the assay) with a calibrator (which has the challenge to continually ensure appropriate value assignment to subsequent lots)?

→ Abbott declares that the use of calibrator improves the alignment with ERM-AD452/IFCC and minimize instrument to instrument variability.

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Two main problems:

1 - The limits for internal validation of ConCC and next generation assay are confused

2 - The use of not commutable Reference Material for trueness transfer process may introduce a bias error increasing the uncertainty of results as for GGT2 happened

IVD manufacturers should implement a trueness transfer process (from higher-order reference to system calibrator) suitable for providing unbiased results by their measuring systems and therefore makes the contribution of systematic bias to the total MU negligible.

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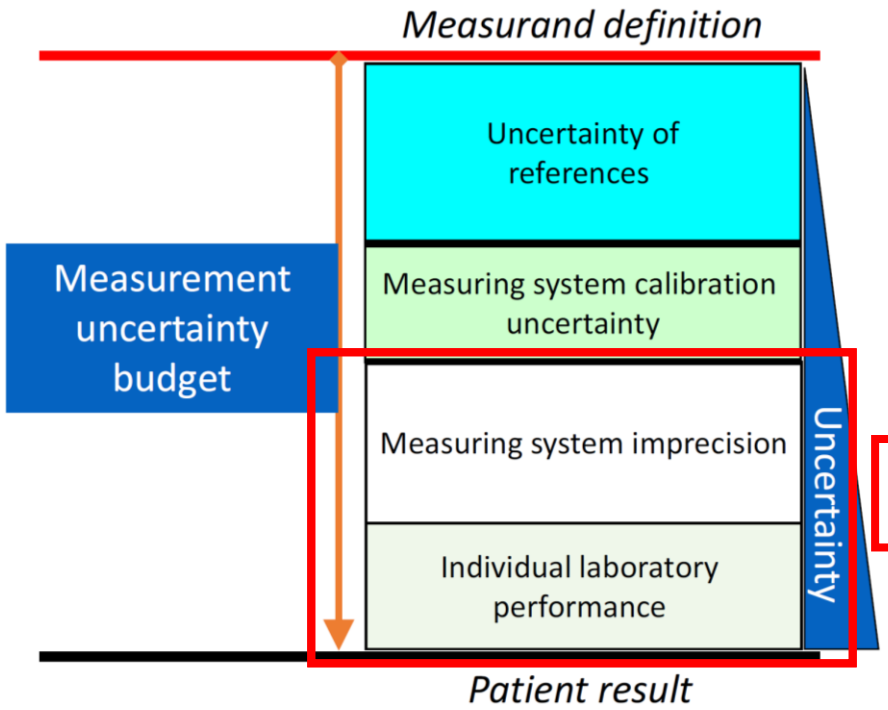
UNCERTAINTY FOR CLINICAL LABORATORIES [u_{Rw}]



Medical laboratory

Variables influencing the u_{Rw}

Measuring system

Reagent lot variability
Calibrator lot variability
Reagent/calibration stability
Measuring equipment

Laboratory using the system

Environmental conditions
Different operators
Instrument maintenance
Material preparation

RANDOM UNCERTAINTY

u_{Rw} gives information about the stability of the measuring system over time and its variability when employed by an individual laboratory

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Braga F et al. CCLM 2021;59:291

Testing MU due to the random effects [u_{Rw}]: using the IQC component II

Table 1: Main characteristics for a control material to be used in the internal quality control component II program in order to derive the uncertainty of the analytical system due to the random effects.

Characteristic	Remarks
Matrixed material from a third-party independent source should be used (e.g., fresh-frozen pool)	Material must be different from the system control material used for checking its alignment
Material should closely resemble to authentic patient samples (fulfil commutability)	Commercial non-commutable controls may provide a different impression of imprecision performance
Material concentrations should be appropriate to the clinical application of the analyte	When clinical decision cut-points are employed for a given analyte, samples around these concentrations should preferentially be selected

1. Provide that the measuring system is running properly and is correctly aligned, through IQC component I data;
2. Run IQC component II material randomly inside the routine analytical run (mimicking analytical conditions of clinical samples);
3. Repeat measurements at least daily for a period (e.g. 6 consecutive months) sufficient to capture most changes in measuring conditions and systematic sources of measurement uncertainty;
4. Do not include gross outliers in the u_{Rw} estimate, but check the measuring system performance and explain the outlier result;
5. At the end of the evaluation period, collect all results and revise the data (exclude explainable outliers, separate data obtained with different lots of control materials, etc.);
6. Calculate mean and SD of replicates;
7. Calculate relative u_{Rw} as SD/mean $\times$ 100

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Clin Chem Lab Med 2015;53:905
Clin Chem Lab Med 2020;58:1407
Clin Chem Lab Med 2021;59:291

Federica Braga* and Mauro Panteghini

Standardization and analytical goals for glycated hemoglobin measurement

Clin Chem Lab Med 2013;51:1719–26

EXAMPLE

Further advances are needed to:

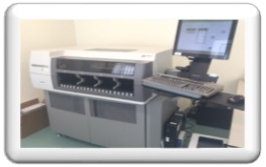
1. reduce uncertainty associated with higher-order metrological references (reference materials and procedures)
2. decrease u_{Rw} of commercial HbA_{1c} assays

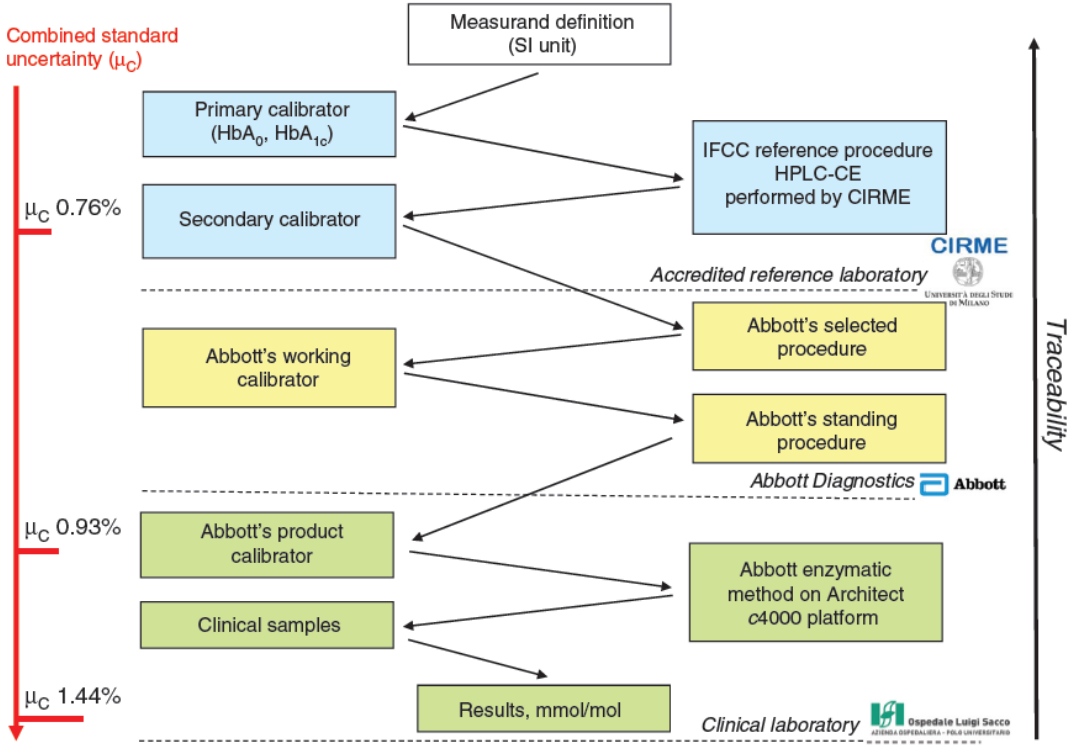
DE GRUYTER Clin Chem Lab Med 2015; aop

Letter to the Editor

Dominika Szőke*, Assunta Carnevale, Sara Pasqualetti, Federica Braga, Renata Paleari and Mauro Panteghini

More on the accuracy of the Architect enzymatic assay for hemoglobin A_{1c} and its traceability to the IFCC reference system





Allowable standard MU	
Desirable	Minimum
3.00%	3.70%

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Measurement uncertainty of thyroid function tests on Abbott Alinity i needs to be improved

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EXAMPLE

Abbott

			Alinity i08				Alinity i09				APS for u_{result}	
	Milan model	**U_{cal} ***	**n**	**Mean**	**u_{Rw}**	**u_{result}**	**n**	**Mean**	**u_{Rw}**	**u_{result}**	**Desirable**	**Minimum**
TSH	State of the art	1.20%	205	13.9 mU/L	5.24%	**5.38%**	218	13.9 mU/L	3.79%	**3.98%**	**2.89%**	**4.34%**
Free T3	Biological variation	1.50%	210	14.3 pmol/L	5.79%	**5.99%**	202	14.3 pmol/L	4.09%	**4.36%**	**2.35%**	**3.53%**
Free T4	Biological variation	0.89%	168	29.5 pmol/L	5.09%	**5.17%**	162	30.0 pmol/L	4.80%	**4.88%**	**2.80%**	**4.20%**

*Manufacturer did not provide the MU corresponding to the employed higher-order references

According to the ISO/TS 20914:2019 for MU estimation,

The main contributor of MU for thyroid function tests on Abbott Alinity assays is u_{Rw}

It is expected that Manufacturer should improve the performance of thyroid function tests on the Alinity i in term of random variability to fulfil clinically suitable APS

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Conclusion

MU is not a finding to be calculated only to fulfil accreditation but must become a Key Quality Indicator to be used to give objective information describe the performance of an IVD measuring system and the laboratory itself

…..in the Standardization Process

- MU gives information about the suitability of metrological traceability chain selected by the IVD manufacturer for implementing traceability of measuring system
- MU may establish if the manufacturers' specifications to validate the calibrator traceability to the selected reference system are enough for the intended use
- MU in clinical laboratories allows the identification of random components of measurement error which may affect the reliability of standardization process

…Together with the MU, valid APS must be define to validate it

Thank you

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Dipartimento di Medicina di Laboratorio
UOC Patologia Clinica

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