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INTERNATIONAL SCIENTIFIC MEETING

Evaluating and monitoring analytical quality in the traceability era

MEASUREMENT UNCERTAINTY AS A KEY PERFORMANCE INDICATOR IN MEDICAL LABORATORIES

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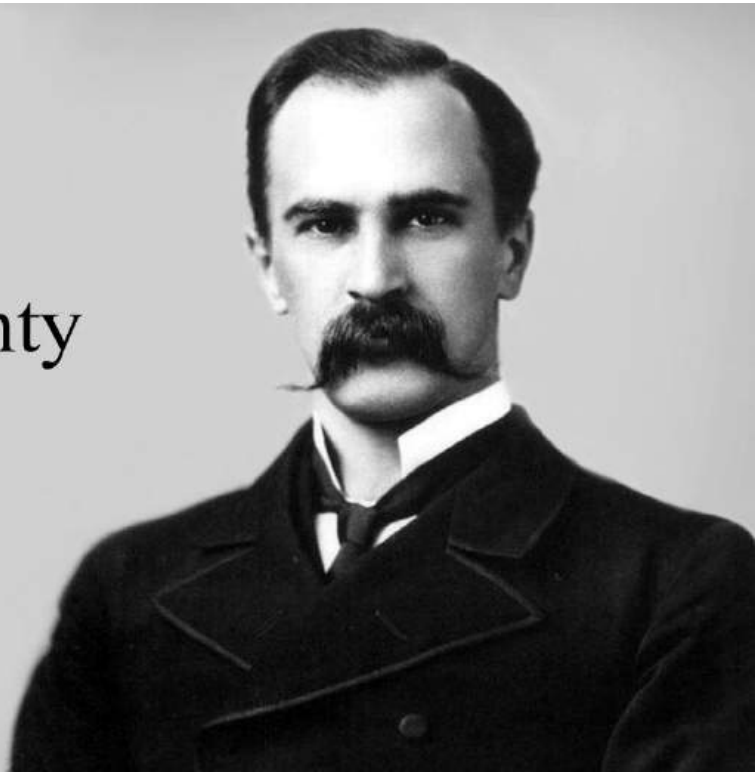
Medicine is a science of uncertainty and an art of probability.

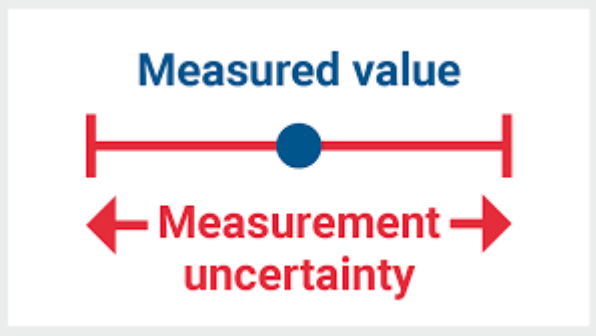
William Osler



Measurement Uncertainty (MU) definition

INTERNATIONAL VOCABULARY OF METROLOGY BASIC AND GENERAL CONCEPTS AND ASSOCIATED TERMS (VIM). 3RD ED. 2012

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



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

Measurement Uncertainty (MU) definition

"…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… "

Result = $x \pm \mu$

Value — Measurement Uncertainty

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

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

Why do we need MU?

The knowledge of MU contributes in producing standardized laboratory results

Laboratory users expect laboratory results to be equivalent, no matter where and how they are obtained, and interpreted in a consistent way

STANDARDIZATION

Unbroken traceability chain
Definition of higher-order references to implement the appropriate trueness transfer process to commercial calibrators and patient results

Measurement Uncertainty
with definition of allowable limits for clinical application of the measurements

Post-marked surveillance
Survey the suitability of IVDs for clinical use and of laboratory performance in using them through appropriate quality control programs

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

Why do we need MU?

ISO 15189:2022 specifies the estimation of measurement uncertainty as a specific requirement for the accreditation of medical laboratories

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

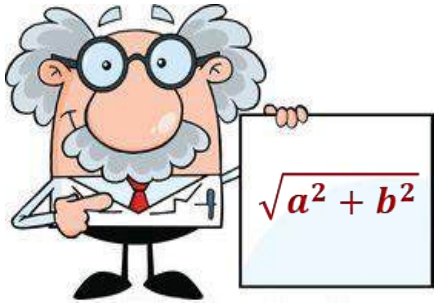
MU is a key quality indicator and it is useful for a number of reasons:

- for giving objective information about the quality of individual laboratory performance;
- for serving as a management tool for the medical laboratory and IVD manufacturers;
- for helping those manufacturers that produce superior products and measuring systems to demonstrate the superiority of those products;
- for identifying analytes that need analytical improvement for their clinical use and ask IVD manufacturers to work for improving the quality of assay performance;
- for abandoning assays with demonstrated insufficient quality.

How to deal with Measurement Uncertainty

Measurement Uncertainty (MU)

MU Estimation



Definition of Analytical Performance Specification for MU

Verification that MU fulfills defined APS

How to calculate MU in medical laboratories

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

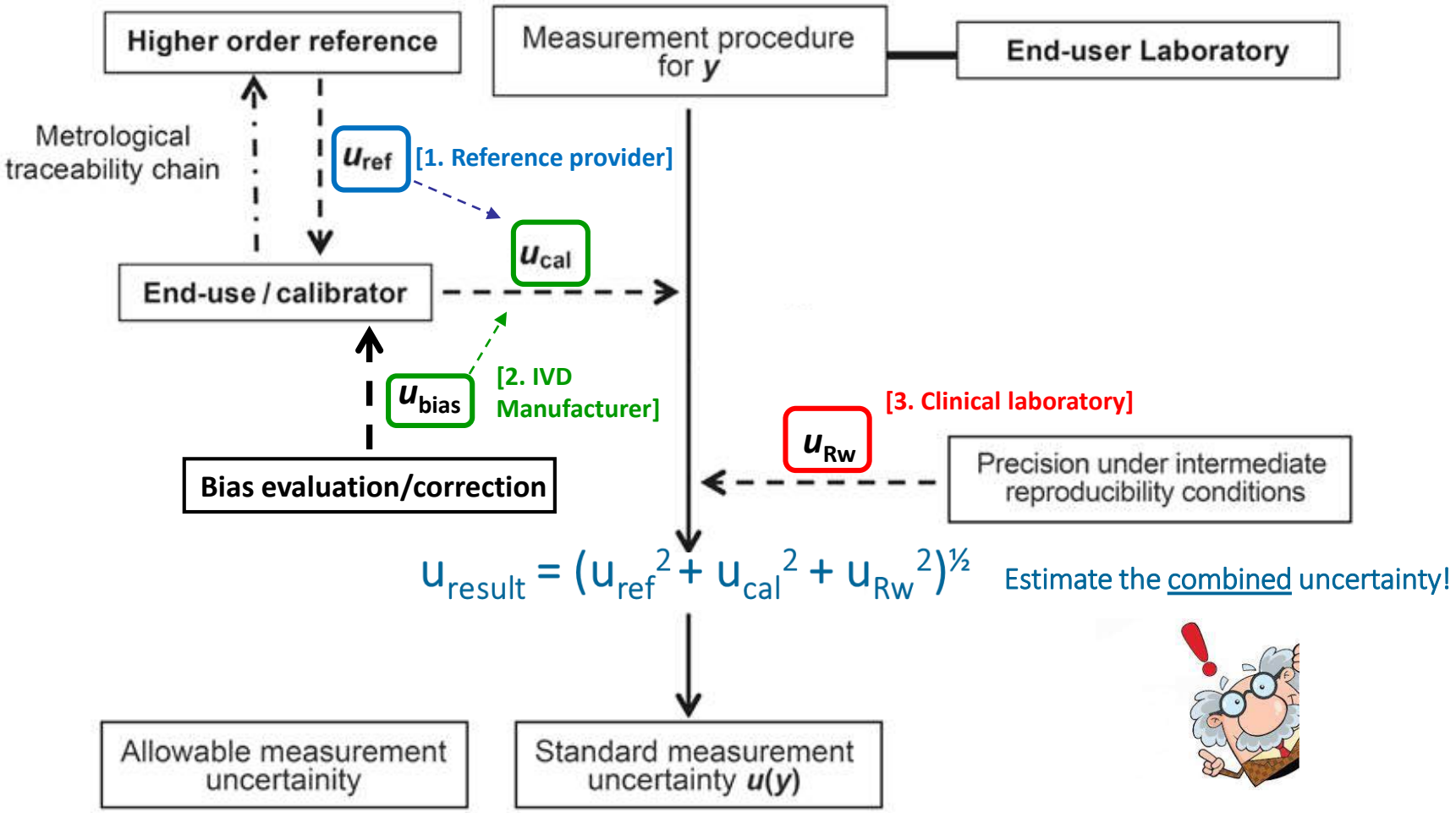
Practical approach to estimation of MU of quantities produced by measurement procedures intended to measure biological measurands, to be applied in medical laboratory

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

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

How to calculate MU in medical laboratories

"Sources of MU with the 'top-down' approach"



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

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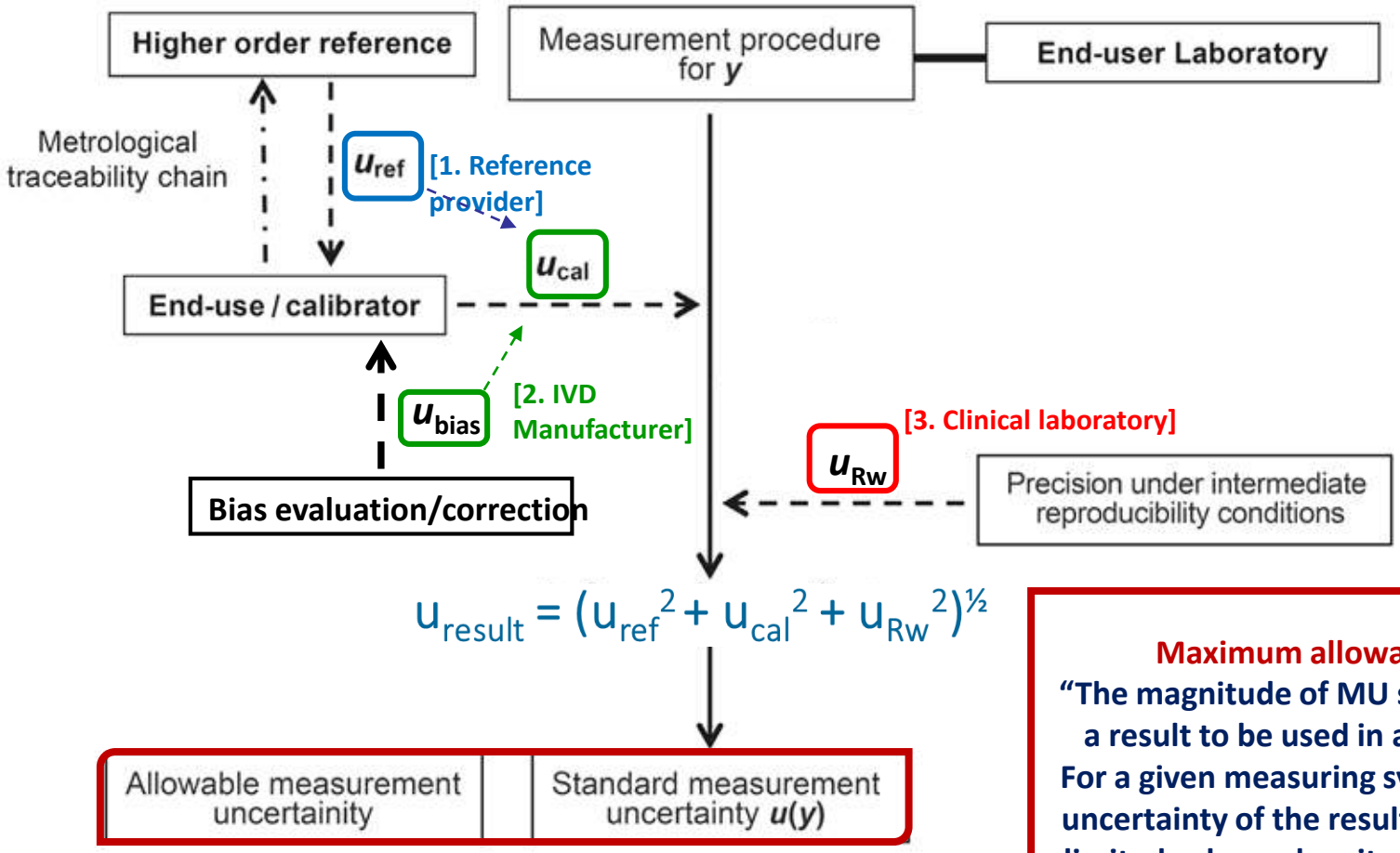
How to calculate MU in medical laboratories



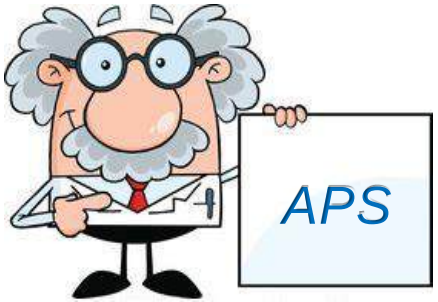
Maximum allowable MU (MAU)

"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

Standardization and target for allowable MU

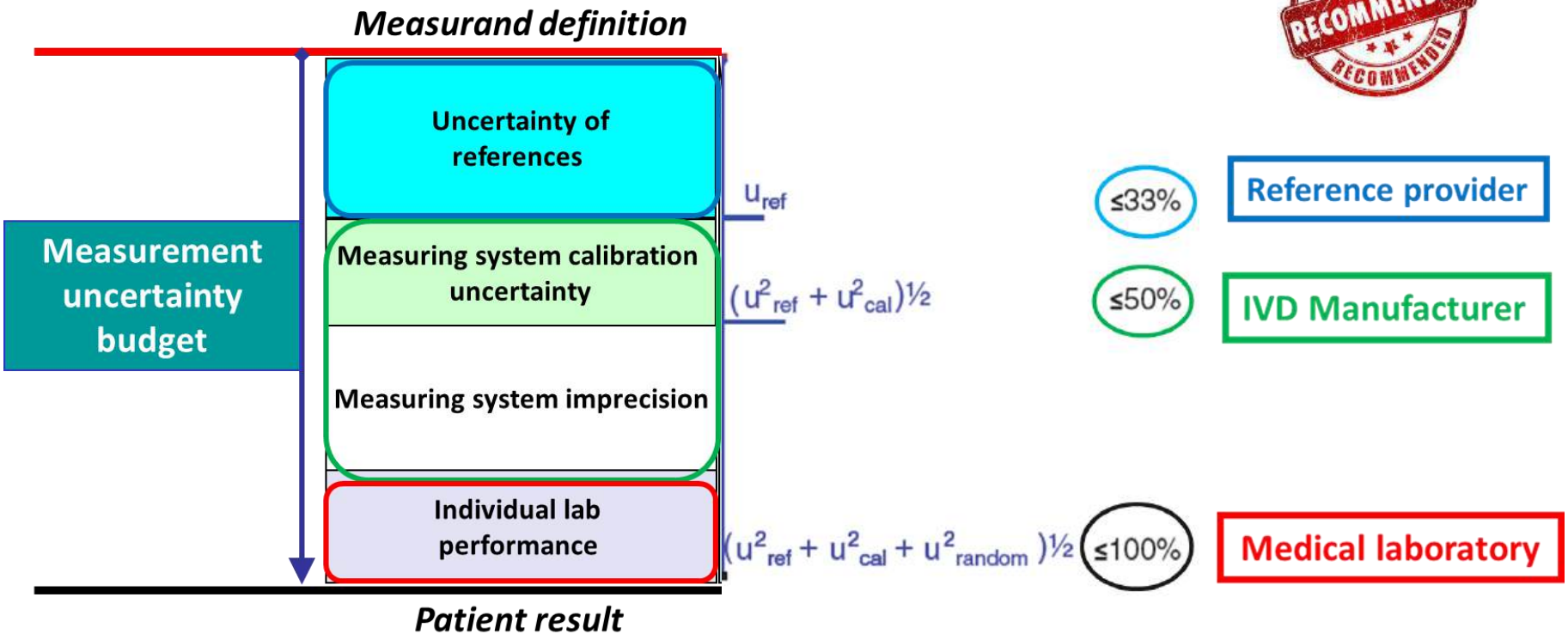
u_{result} *must fulfill APS*



If these goals are not objectively defined and fulfilled, there is a risk of letting error gain the upper hand, thus obscuring the clinical information supplied by the result and possibly nullifying the theoretical advantages of metrological traceability and even causing negative effects on patients' outcome.

Standardization and target for allowable MU

RECOMMENDED LIMITS EXPRESSED AS PERCENTAGE OF TOTAL MU BUDGET GOAL



Braga F, Panteghini M. Clin Chem Lab Med. 2015 May;53(6):905-12.

APERTURE PROJECT

Sistema Socio Sanitario

Regione Lombardia

ASST Fatebenefratelli Sacco

CIRME

Università degli Studi di Milano

Ospedale Luigi Sacco

Azienda Ospedaliera - Polo Universitario

A project for establishing Analytical Performance Specifications for Measurement Uncertainty of common measurands based on Milan models

APERTURE PROJECT

Moving from theoretical principles to practice…

Step 1	• 50 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

50 measurands tested

ALINITY c (Abbott)

- Plasma glucose
- Blood HbA1c
- Serum creatinine
- Serum urea
- Serum urate
- Serum sodium
- Serum potassium
- Serum chloride
- Serum total carbon dioxide
- Serum total calcium
- Serum phosphate
- Serum magnesium
- Serum total bilirubin
- Serum conjiugated bilirubin
- Plasma lactate
- Serum transferrin saturation
- Serum ethanol
- Serum total cholesterol
- Serum HDL cholesterol
- Serum triglycerides
- Serum ALT
- Serum AST
- Serum alkaline phosphatase
- Serum creatine kinase
- Serum γ-glutamyltransferase
- Serum LDH
- Serum lipase
- Serum pancreatic amylase
- Serum cholinesterase
- Serum albumin
- Urine albumin
- Urine total protein
- Serum C-reactive protein
- Serum digoxin

ALINITY i (Abbott)

- Plasma homocysteine
- Serum TSH
- Serum hCG

COBAS e801 (Roche)

- Serum PSA
- Serum total folate
- Serum cardiac troponin T

XN-9000 (Sysmex)

- Blood total hemoglobin
- Red blood cells
- White blood cells
- Platelets

AU680 (Beckman Coulter)

- Serum total protein
- Serum IgG
- Serum IgA
- Serum IgM

ACL TOP 750 (Werfen)

- D-dimer

Liaison (DiaSorin)

- Serum 25-hydroxyvitamin D3

Step 2

APERTURE PROJECT

MODEL 1 Outcome-based model
Fasting plasma glucose
Blood HbA_{1c}
Blood total hemoglobin
Serum total cholesterol
Serum HDL cholesterol
Serum triglycerides
Serum cardiac troponin
Urine albumin
Serum total folate
Serum 25-hydroxyvitamin D_3
Serum transferrin saturation

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

Step 2

APERTURE PROJECT

MODEL 2
Biological Variation model

Serum sodium	Serum γ-glutamyltransferase
Serum potassium	Serum lactate dehydrogenase
Serum chloride	Serum cholinesterase
Serum total carbon dioxide	Serum total proteins
Serum total calcium	Serum IgG
Serum inorganic phosphate	Serum IgA
Serum magnesium	Serum IgM
Serum creatinine	Serum prostate-specific antigen
Serum urea	Plasma homocysteine
Serum urate	Red blood cells
Plasma lactate	White blood cells
Serum total bilirubin	Serum conjiugated bilirubin
Serum alkaline phosphatase	
Serum aspartate aminotransferase	

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 CVI estimates needed to calculate APS for MU

Temporarily belonging to biological variation model

Serum albumin
Plasma D-dimer
Blood platelets
Serum alanine aminotransferase
Serum creatine kinase
Serum pancreatic lipase
Serum pancreatic amylase

For these measurands, 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

APERTURE PROJECT

MODEL 3
State of the art model

Serum C-reactive protein
Serum intact human chorionic gonadotropin

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

Temporarily belonging to MODEL 3
State of the art model

Serum thyroid stimulating hormone
Urine total protein
Serum ethanol

Because outcome-based data are lacking we temporarily allocated those measurands to to the state-of-the-art .

Step 2

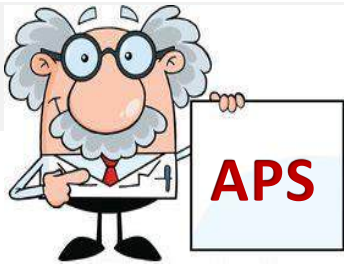
APERTURE PROJECT

MODEL 1&2
Serum digoxin

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



Measurand	u_{result} APS, %		u_{cal} APS, %[a]		u_{ref} APS, %[b]	
	Desirable	Minimum	Desirable	Minimum	Desirable	Minimum
Outcome-based model						
Fasting plasma glucose	2.00	3.00	1.00	1.50	0.67	1.00
Blood HbA_{1c}	3.00	3.70	1.50	1.85	1.00	1.23
Blood total hemoglobin	5.60	8.50	2.80	4.25	1.87	2.83
Serum total cholesterol	3.00	7.00	1.50	3.50	1.00	2.33
Serum HDL cholesterol	2.90	5.60	1.45	2.80	0.97	1.87
Serum triglycerides	6.10	12.4	3.05	6.20	2.03	4.13
Serum cardiac troponin	9.40	13.0	4.70	6.50	3.13	4.33
Urine albumin	9.00	17.0	4.50	8.50	3.00	5.67
Serum total folate	8.00	12.0	4.00	6.00	2.67	4.00
Serum 25-hydroxyvitamin D_3	10.0	15.0	5.00	7.50	3.33	5.00
Serum transferrin saturation	10.0	15.0	5.00	7.50	3.33	5.00
Temporarily belonging to biological variation model[c]						
Serum albumin	1.25	1.88	0.63	0.94	0.42	0.63
Plasma D-dimer	10.6	15.9	5.30	7.95	3.53	5.30
Blood platelets	4.85	7.28	2.43	3.64	1.62	2.43
Serum alanine aminotransferase	4.65	6.98	2.33	3.49	1.55	2.33
Serum creatine kinase	7.25	10.9	3.63	5.45	2.42	3.63
Serum pancreatic lipase	3.85	5.78	1.93	2.89	1.28	1.93
Serum pancreatic amylase	3.15	4.73	1.58	2.37	1.05	1.58

Biological variation model						
Serum sodium	0.27	0.40	0.14	0.20	0.09	0.13
Serum potassium	1.96	2.94	0.98	1.47	0.65	0.98
Serum chloride	0.49	0.74	0.25	0.37	0.16	0.25
Serum total carbon dioxide	2.10	3.15	1.05	1.58	0.70	1.05
Serum total calcium	0.91	1.36	0.46	0.68	0.30	0.45
Serum inorganic phosphate	3.84	5.75	1.92	2.88	1.28	1.92
Serum magnesium	1.44	2.16	0.72	1.08	0.48	0.72
Serum creatinine	2.20	3.30	1.10	1.65	0.73	1.10
Serum urea	7.05	10.6	3.53	5.30	2.35	3.53
Serum urate	4.16	6.24	2.08	3.12	1.39	2.08
Plasma lactate	13.6	20.4	6.80	10.2	4.53	6.80
Serum total bilirubin	10.5	15.7	5.25	7.85	3.50	5.23
Serum alkaline phosphatase	2.65	3.98	1.33	1.99	0.88	1.33
Serum aspartate aminotransferase	4.75	7.13	2.38	3.57	1.58	2.38
Serum γ-glutamyltransferase	4.45	6.68	2.23	3.34	1.48	2.23
Serum lactate dehydrogenase	2.60	3.90	1.30	1.95	0.87	1.30
Serum cholinesterase	2.10	3.15	1.05	1.58	0.70	1.05
Serum total proteins	1.30	1.95	0.65	0.98	0.43	0.65
Serum IgG	2.20	3.30	1.10	1.65	0.73	1.10
Serum IgA	2.50	3.75	1.25	1.88	0.83	1.25
Serum IgM	2.95	4.43	1.48	2.22	0.98	1.48
Serum prostate-specific antigen	3.40	5.10	1.70	2.55	1.13	1.70
Plasma homocysteine	3.52	5.27	1.76	2.64	1.17	1.76
Red blood cells	1.55	2.33	0.78	1.17	0.52	0.78
White blood cells	5.65	8.48	2.83	4.24	1.88	2.83
Serum conjiugated bilirubin	10.5	15.7	5.25	7.85	3.50	5.23
State-of-the-art model						
Serum C-reactive protein	3.76	5.64	1.88	2.82	1.25	1.88
Serum intact human chorionic gonadotropin	4.55	6.83	2.28	3.42	1.52	2.28

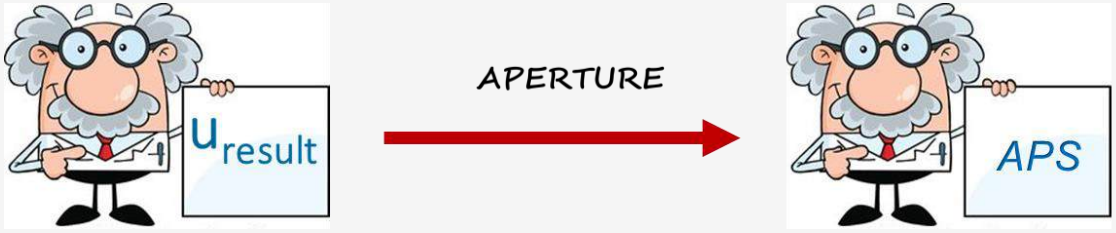
Temporarily belonging to state-of-the-art model[d]						
Serum ethanol	3.11	4.67	1.56	2.33	1.03	1.55
Serum thyroid stimulating hormone	2.89	4.34	1.45	2.17	0.96	1.45
Urine total protein	4.97	7.46	2.49	3.73	1.66	2.49
Model 1&2[e]						
Serum digoxin	6.00	9.00	3.00	4.50	2.00	3.00

"How many measurands can achieve the recommended MAU and can the available IVD-MDs hit these targets?"

50 measurands were selected and their u_{result} were estimated in a medical laboratory using commercial platforms as described in ISO/TS 20914:2019, by employing internal quality control data to derive u_{Rw} and u_{cal} information provided by the manufacturers

Step 4

APERTURE PROJECT



The results showed that the great majority of evaluated tests (90%) fulfilled at least the minimum MAU

30 measurands — HITTING DESIRABLE MAU

15 measurands — HITTING MINIMUM MAU

5 measurands — UNACCEPTABLE MU

- Serum sodium
- Serum chloride
- Serum total carbon dioxide
- Serum albumin
- Plasma homocysteine

How to deal when MU is out of APS

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

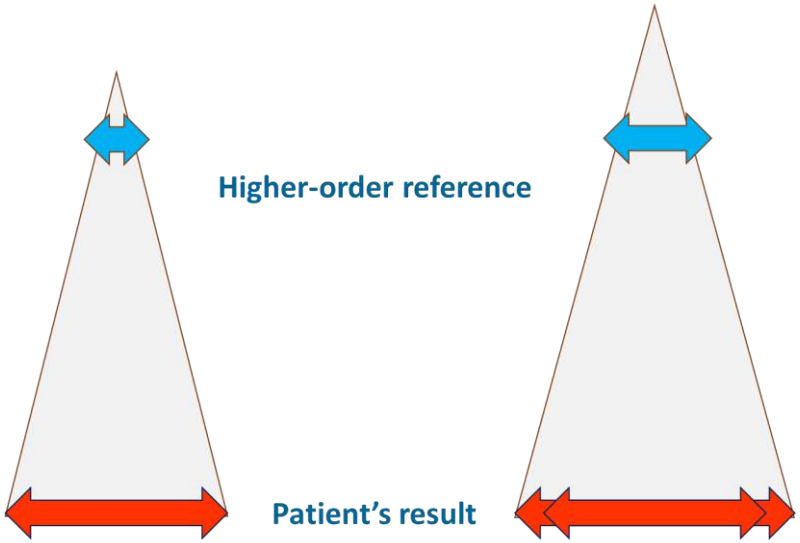
Reference provider

↓

≤33%

↓

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



Braga F, Panteghini M. Clin Chem Lab Med. 2015 May;53(6):905-12.

EXAMPLE How to deal when MU is out of APS

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

SERUM CREATININE

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

0.75%
Desirable

1.1%
Minimum

JCTLM

Access July 2019

Secondary RM/RMP	Traceability of assigned values	Nominal value, µmol/L	Combined standard uncertainty, %[a]	Commutability information
JRC BCR-573 (lyophilized human serum)	By ID/GC/MS and HPLC[b] calibrated with the NIST SRM 914a	68.7	*1.02*	Not available
JRC BCR-574 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	105.0	**0.62**	Not available
JRC BCR-575 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	404.1	*0.88*	Not available
LGC ERM-DA250a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	358.0	5.87	Not available
LGC ERM-DA251a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	197.0	5.58	Not available
LGC ERM-DA252a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	27.5	15.6	Not available
LGC ERM-DA253a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	449.0	3.56	Not available
LNE CRM Bio 101a level 1 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	53.04	*1.09*	Available
LNE CRM Bio 101a level 2 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	550.54	**0.56**	Available
CENAM DMR-263a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914a	66.4	2.18	Not available
ID/GC/MS	By calibration with high purity crystalline creatinine	151.9[c] 352.9[c]	**0.49**[c] **0.50**[c]	By definition
ID/LC/MS	By calibration with high purity crystalline creatinine	152.1[d] 350.5[d]	*0.82*[d] **0.40**[d]	By definition
ID/SERS	By calibration with high purity crystalline creatinine	345.7[e] 492.0[e]	1.23[e] 2.24[e]	By definition

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.

Panteghini M, Braga F. Implementation of metrological traceability in laboratory medicine: where we are and what is missing. Clin Chem Lab Med. 2020 Jul 28;58(8):1200-1204.

EXAMPLE

How to deal when MU is out of APS

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

PLASMA SODIUM

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%
Plasma Na: 160 mmol/L		MAU 0.41%

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%
Plasma Na: 160 mmol/L		MAU 0.41%

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

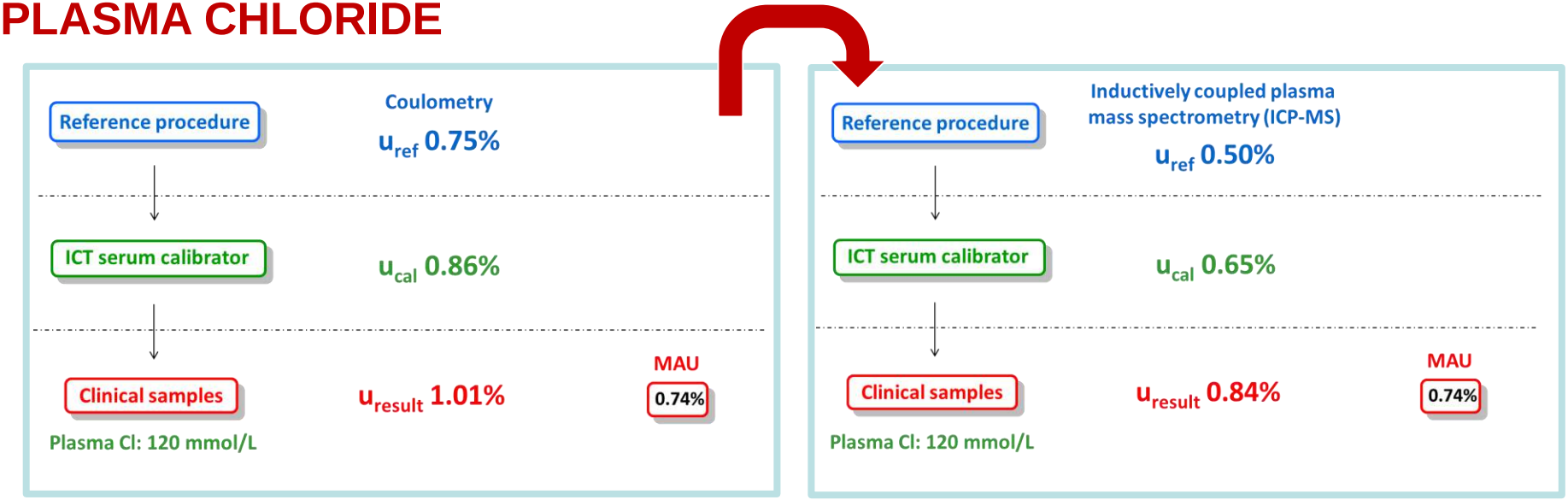
"By replacing flame emission spectrophotometry with ion chromatography in the Na value-assigning process of Abbott calibrators, u_{result} on Alinity measuring system could be improved from about 0.80% to 0.55%."

Pasqualetti S, Chibireva M, Borrillo F, Braga F, Panteghini M. Improving measurement uncertainty of plasma electrolytes: a complex but not impossible task. Clin Chem Lab Med. 2020 Oct 13;59(4):e129-e132.

EXAMPLE How to deal when MU is out of APS

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

PLASMA CHLORIDE



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.

Pasqualetti S, Chibireva M, Borrillo F, Braga F, Panteghini M. Improving measurement uncertainty of plasma electrolytes: a complex but not impossible task. Clin Chem Lab Med. 2020 Oct 13;59(4):e129-e132.

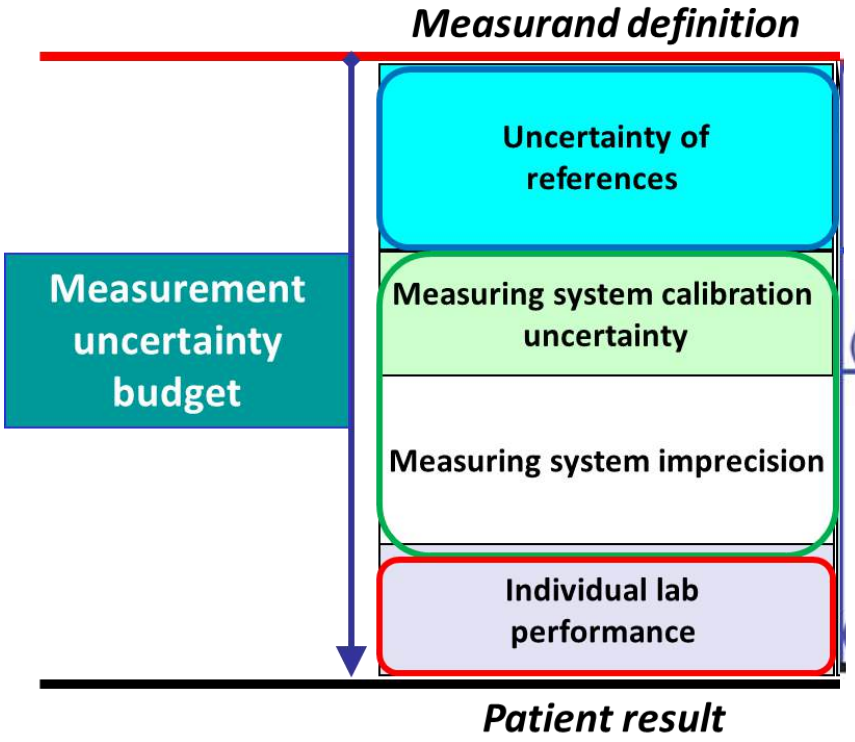
How to deal when MU is out of APS

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

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.

How to deal when MU is out of APS

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



$(u^2_{ref} + u^2_{cal})^{1/2}$ → ≤50% → IVD Manufacturer

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!

Braga F, Panteghini M. Clin Chem Lab Med. 2015 May;53(6):905-12.

How to deal when MU is out of APS

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

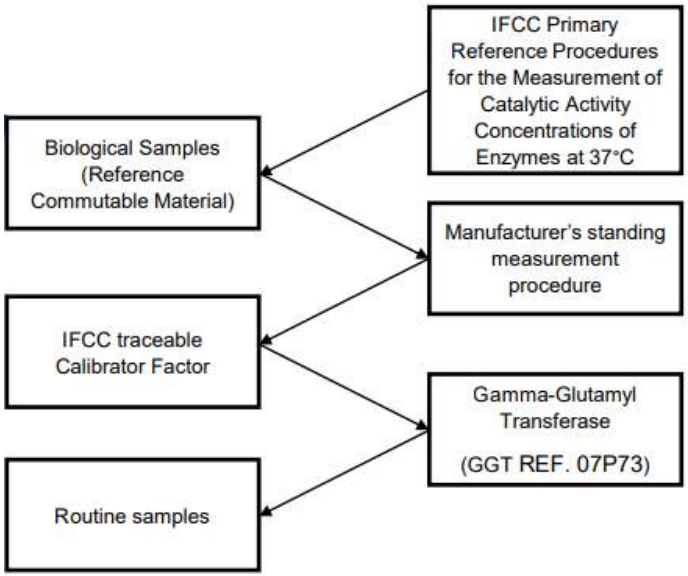
Abbott

GGT1

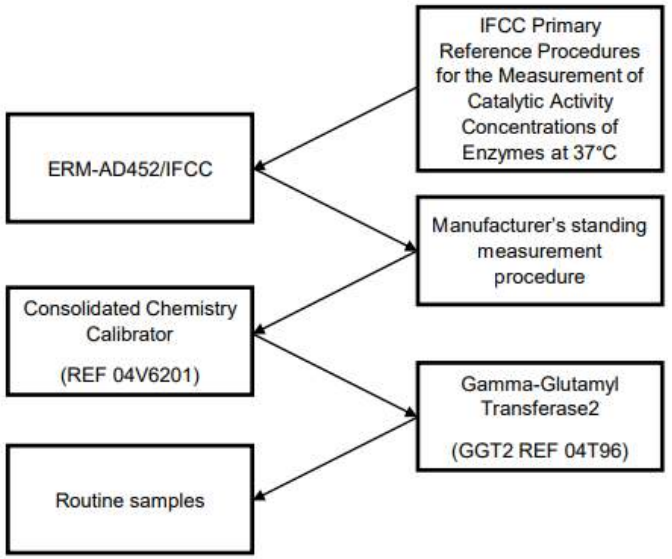
Abbott GmbH & Co. KG
Max-Planck-Ring 2
65205 Wiesbaden
Germany

Abbott Ireland
Diagnostics Division
Lisnamuck, Longford
Co. Longford
Ireland

GGT2



IFCC Standardized Calibration Factor



Consolidated Chemistry Calibrator (ConCC)

Bianchi G, Colombo G, Pasqualetti S, Panteghini M. Alignment of the new generation of Abbott Alinity γ-glutamyltransferase assay to the IFCC reference measurement system should be improved. Clin Chem Lab Med. 2022 Aug 9;60(10):e228-e231.

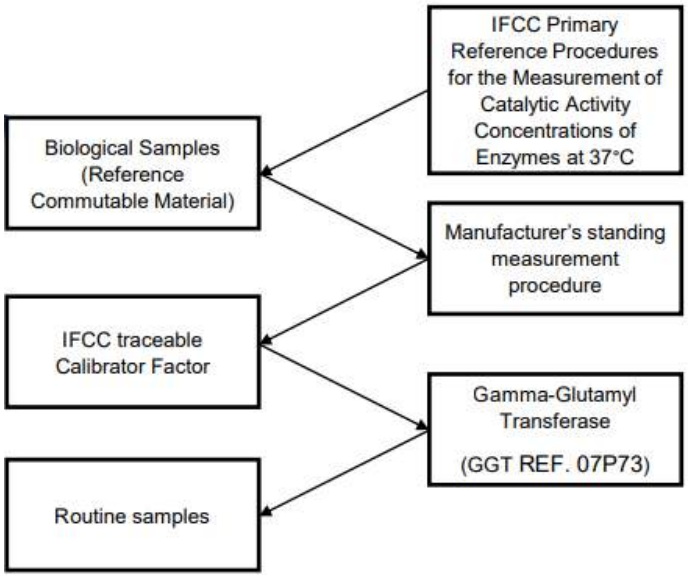
How to deal when MU is out of APS

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

CLSI EP9-A3

GGT1

Abbott

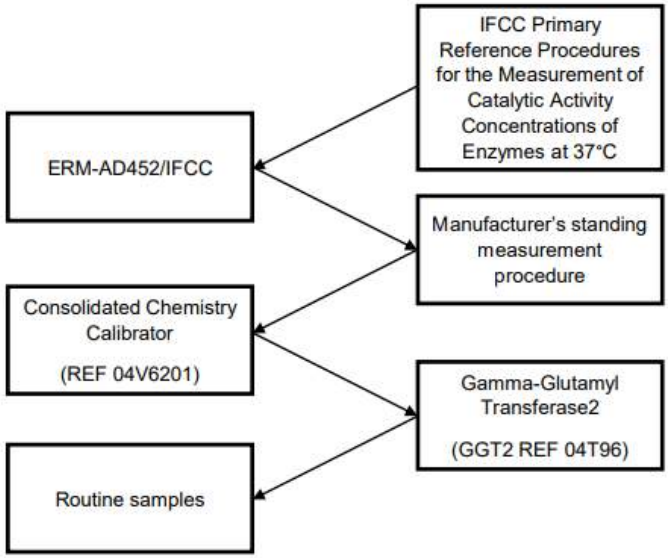


IFCC Standardized Calibration Factor

VS

GGT2

Abbott



Consolidated Chemistry Calibrator (ConCC)

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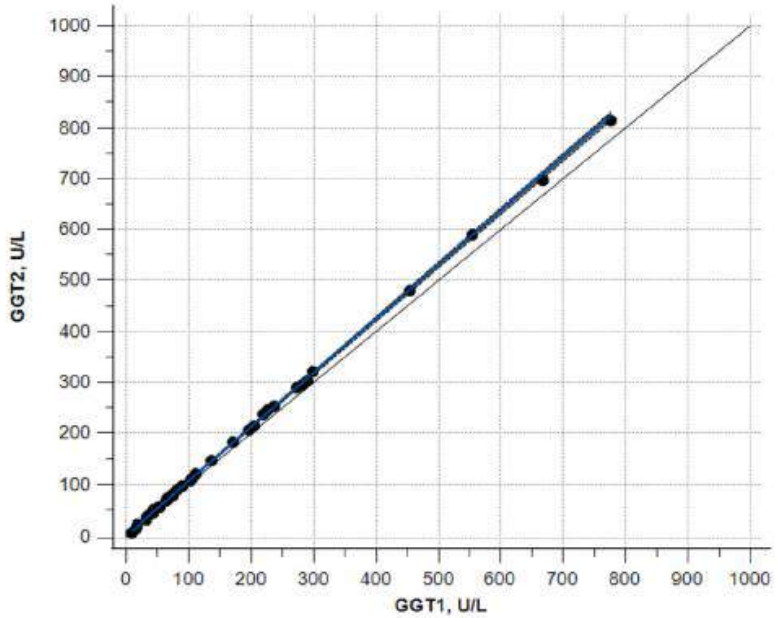
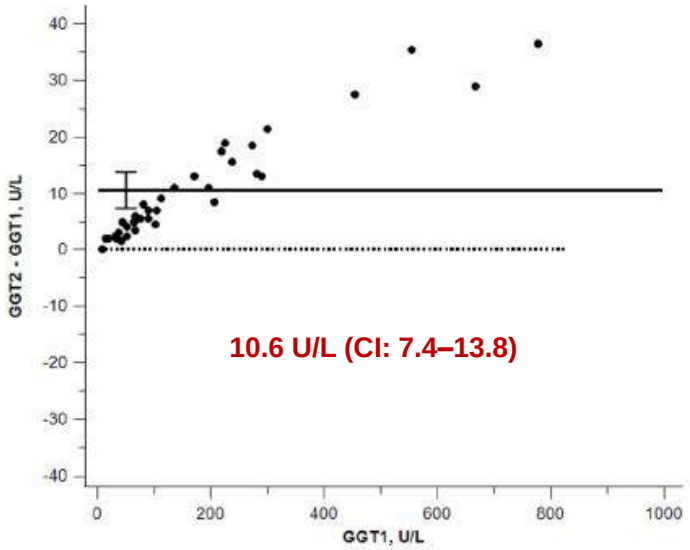
How to deal when MU is out of APS

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

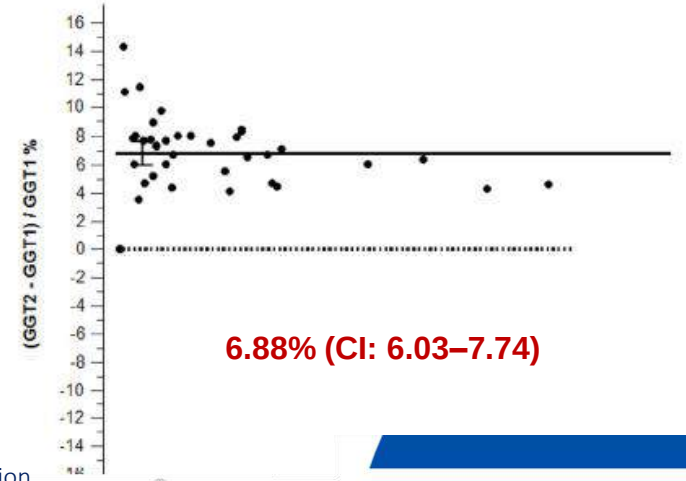
CLSI EP9-A3



GGT2=1.061 (95%CI: 1.050–1.069) GGT1 + 0.9 (95%CI: 0.1–1.6) U/L]



10.6 U/L (CI: 7.4–13.8)



6.88% (CI: 6.03–7.74)

Bianchi G, Colombo G, Pasqualetti S, Panteghini M. Alignment of the new generation of Abbott Alinity γ-glutamyltransferase assay to the IFCC reference measurement system should be improved. Clin Chem Lab Med. 2022 Aug 9;60(10):e228-e231.

How to deal when MU is out of APS

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

CIRME

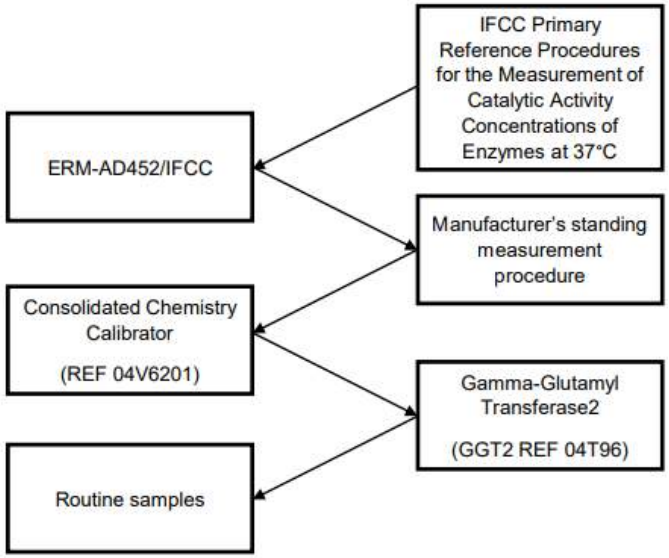
UNIVERSITÀ DEGLI STUDI DI MILANO

Schumann G. et al. IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzyme at 37 degrees C. Part 6 Reference procedure for measurement of catalytic concentration of gamma-glutamyltransferase. Clin Chem Lab Med 2002; 40:734-8.

VS

GGT2

Abbott



Consolidated Chemistry Calibrator (ConCC)

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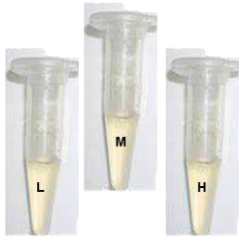
How to deal when MU is out of APS

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



Pool ID	RMP	
	Target, U/L	u_{ref}, U/L
L	43.0	0.75
M	84.3	1.13
H	211.3	2.87

Mean of three Alinity GGT2 replicates, U/L	Bias, U/L	2*u_{bias}, U/L[a]	Bias, %	Regression parameters
46.0	3.0	1.5	6.98	y=1.089x – 0.8 U/L, R^2=1.0000
89.7	5.4	2.4	6.41	
230.0	18.7	6.2	8.85	

Mean Bias = 7,41%

An estimate of measurement bias is considered statistically significant if: Bias > 2 x u_{bias}

$ubias=\sqrt{uref + SDmean^2}$

where SDmean is the standard deviation of the mean value of each pool measured by GGT assay calculated as SD/√n, in which SD is the standard deviation of the triplicate measurement of the pool and n=3.

$u_{result} = \sqrt{(bias^2 + u_{bias}^2 + u_{cal}^2 + u_{Rw}^2)} = 9.14\%$

Minimum MU APS: 6.68%

"The presence of a positive proportional bias when GGT2 is employed may denote some problems in the ConCC value-assignment protocol used for transferring trueness from higher-order references to ConCC"

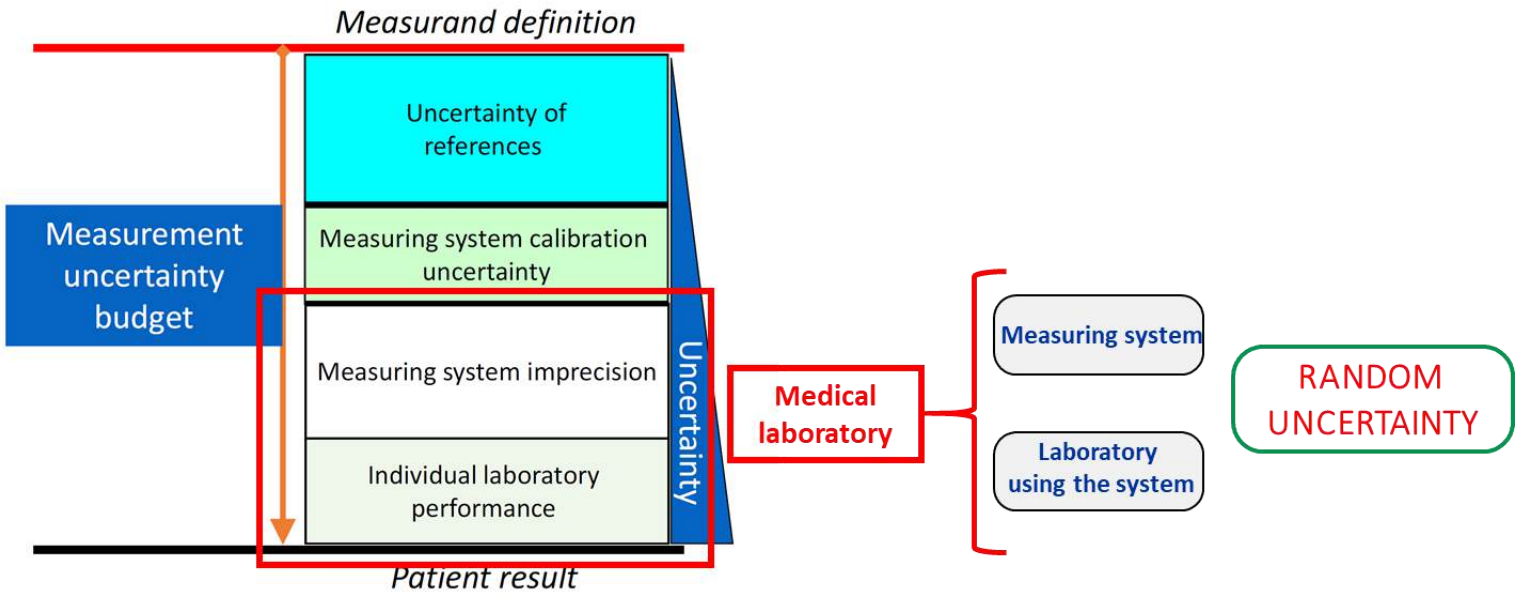
How to deal when MU is out of APS

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

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.

How to deal when MU is out of APS

UNCERTAINTY FOR CLINICAL LABORATORIES (u_{Rw})



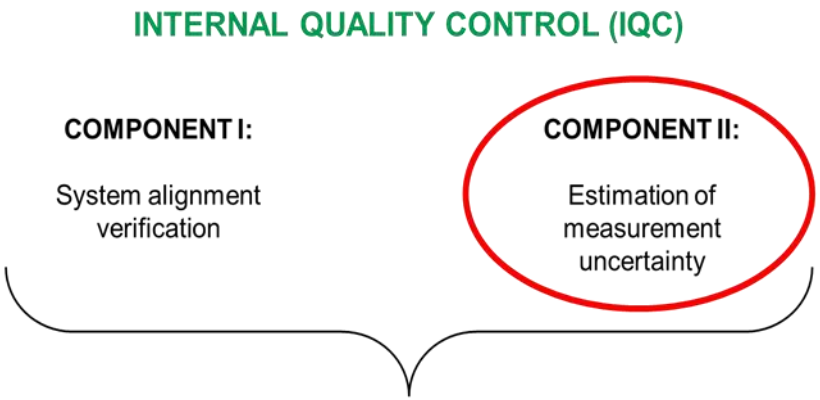
System imprecision + **Individual lab performance**

- Reagent lot variability
- Calibrator lot variability
- Reagent/Calibration stability
- Measuring equipment
- Environmental conditions
- Different operators
- Instrument maintenance
- Material preparation

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

How to deal when MU is out of APS

Testing MU due to the random effects (uRw): using the IQC component II



CONTROL MATERIALS:

- Third Party
- Commutable
- Clinically relevant concentrations

INTERMEDIATE PRECISION:

- Consecutive 6-month evaluation

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 × 100

Braga, Federica, Pasqualetti, Sara, Aloisio, Elena and Panteghini, Mauro. "The internal quality control in the traceability era" Clinical Chemistry and Laboratory Medicine (CCLM), vol. 59, no. 2, 2021, pp. 291-300

EXAMPLE

How to deal when MU is out of APS

UNCERTAINTY FOR CLINICAL LABORATORIES (u_{Rw})

… about the stability of the measuring system over time

Meaurement uncertainty of thyroid function tests on the Abbott Alinity i platform.

		Alinity i08				Alinity i09				Between platforms				Allowable measurement uncertainty on clinical samples[a]	
	u_{cal}	n^b	Mean	u_{Rw}	u_{result}^c	n^b	Mean	u_{Rw}	u_{result}^c	n^b	Mean	u_{Rw}	u_{result}^c	Desirable quality	Minimum quality
TSH	1.20%[d]	205	14.1 mU/L	5.24%	**5.38%**	218	13.9 mU/L	3.79%	*3.98%*	423	14.0 mU/L	4.62%	**4.77%**	2.89%	4.34%
fT3	1.50%[e]	210	14.3 pmol/L	5.79%	**5.99%**	202	14.3 pmol/L	4.09%	**4.36%**	412	14.3 pmol/L	5.02%	**5.24%**	2.35%	3.53%
fT4	0.89%[f]	168	29.5 pmol/L	5.09%	**5.17%**	162	30.0 pmol/L	4.80%	**4.88%**	330	29.8 pmol/L	5.01%	**5.09%**	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

Borrillo F, Pasqualetti S, Panteghini M. Measurement Uncertainty of Thyroid Function Tests on a Chemiluminescent Microparticle Immunoassay System Needs to Be Improved. J Appl Lab Med. 2023 Mar 6;8(2):420-422

How to deal when MU is out of APS

UNCERTAINTY FOR CLINICAL LABORATORIES (u_{Rw})

It is expected that individual laboratory should critically review the data during/at the end of the evaluation period. Medium/long term evaluation is necessary in order to account for most sources of analytical variation.

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

Reference provider

- MU gives information about the suitability of metrological traceability chain selected by the IVD manufacturer for implementing traceability of measuring system

IVD Manufacturer

- MU may establish if the manufacturers' specifications to validate the calibrator traceability to the selected reference system are enough for the intended use

Medical laboratory

- 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 FOR ATTENTION

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Fatebenefratelli-Sacco, Milan, Italy