Uncertainty in Laboratory Medicine

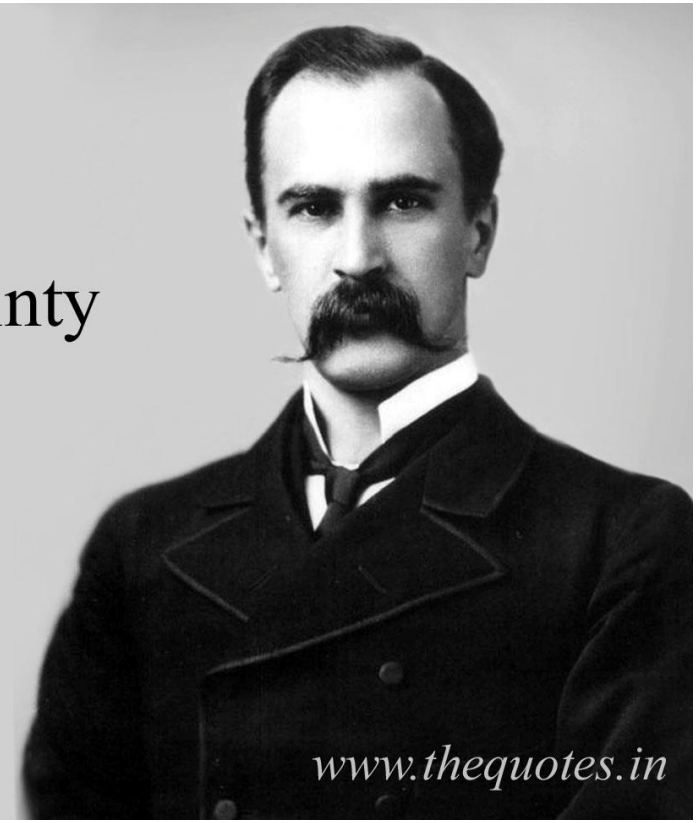
October 28th, 2019

Mario Plebani
University-Hospital
of Padova, Italy

CERTAINTY IS AN ILLUSION

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

William Osler



CERTAINTY IS AN ILLUSION

….and despite significant advances in diagnostic testing, physicians still face ***uncertainty in interpretation.***

As the historic paradigm of estimating pretest probability, followed by laboratory tests to refine the likelihood of disease, frequently no longer applies, new approaches are needed to remind clinicians that ***results*** should be ***considered in relation to*** the ***clinical*** impression and ***context.***

Whyte MB, Vincent RP. Emerg Med J. 2016

THE DIAGNOSTIC PROCESS

The diagnostic process is a ***complex***, ***patient-centered***, ***collaborative activity*** that involves ***information gathering*** and ***clinical reasoning*** with the goal of determining a patient's health problem.

Improving diagnosis in health care. National Academies of Sciences, Engineering and Medicine, 2015

INFORMATION GATHERING

The goal of information gathering in the diagnostic process is to ***reduce diagnostic uncertainty*** enough to make ***optimal decisions*** for subsequent care (J Kassirer, 1989)

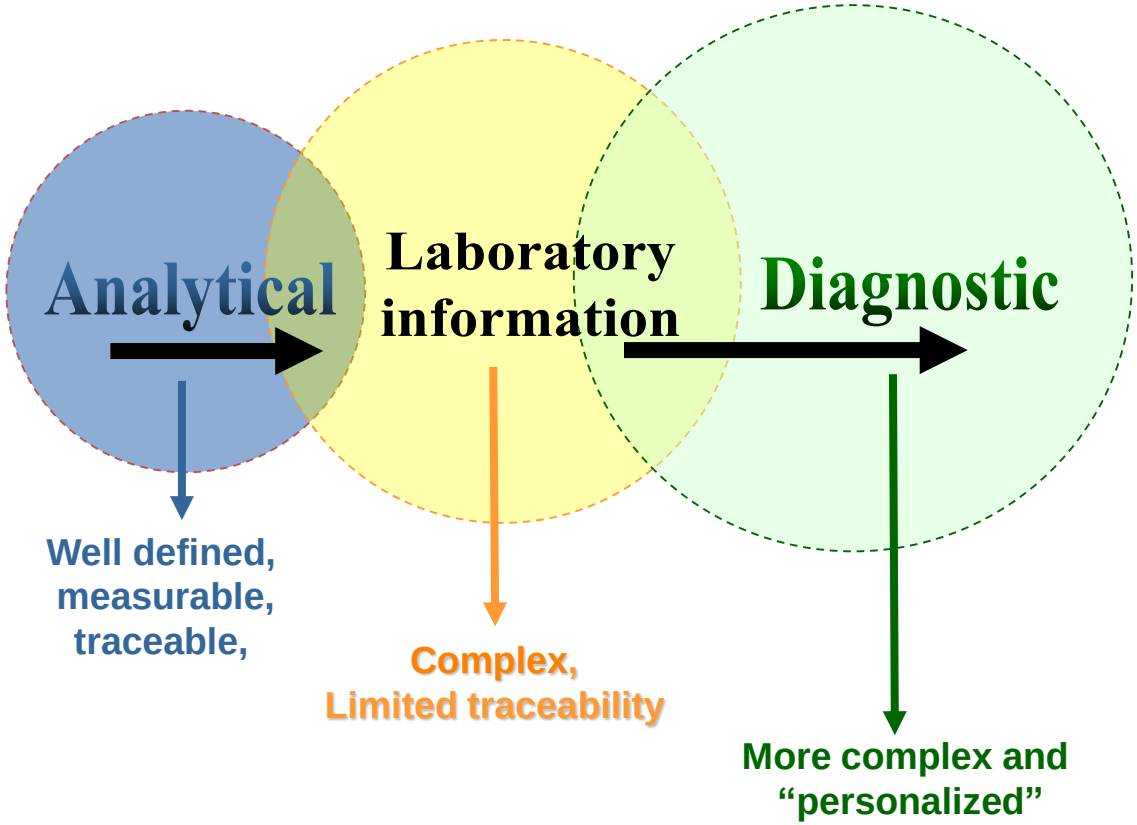
There are ***four types*** of ***information gathering*** activities in the diagnostic process: 1) taking a clinical history and interview, 2) performing a physical exam; 3) ***obtaining diagnostic testing***; and 4) sending a patient for referrals or consultations.

CLINICAL REASONING

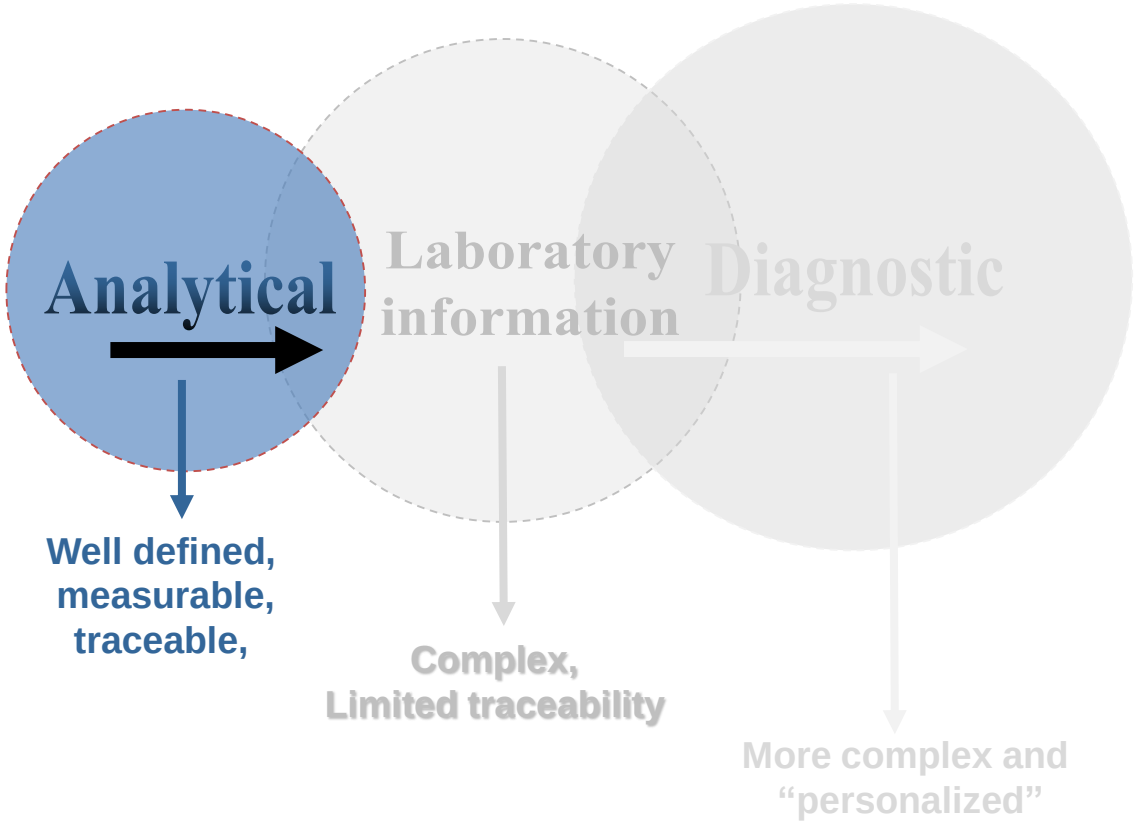
Clinical reasoning is «the cognitive process that is necessary to evaluate and manage a patient's medical problems».

Clinical reasoning occurs within clinicians' minds (facilitated or impeded by work system) and involves judgment under uncertainty, with a consideration of possible diagnoses that may explain symptoms and signs, the ***harm*** and ***benefits of diagnostic testing***…….

UNCERTAINTY



UNCERTAINTY



EN ISO 15189:2003

INTERNATIONAL STANDARD

ISO 15189

First edition
2003-02-15

EN ISO 15189:2007

INTERNATIONAL STANDARD

ISO 15189

Second edition
2007-04-15

BS EN ISO 15189:2012

Incorporating corrigendum October 2014

BSI Standards Publication

Medical laboratories — Requirements for quality and competence (ISO 15189:2012)

Measurement uncertainty

ISO 15189 and MEASUREMENT UNCERTAINTY

ISO 15189: 2012,5.5.1.4 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"

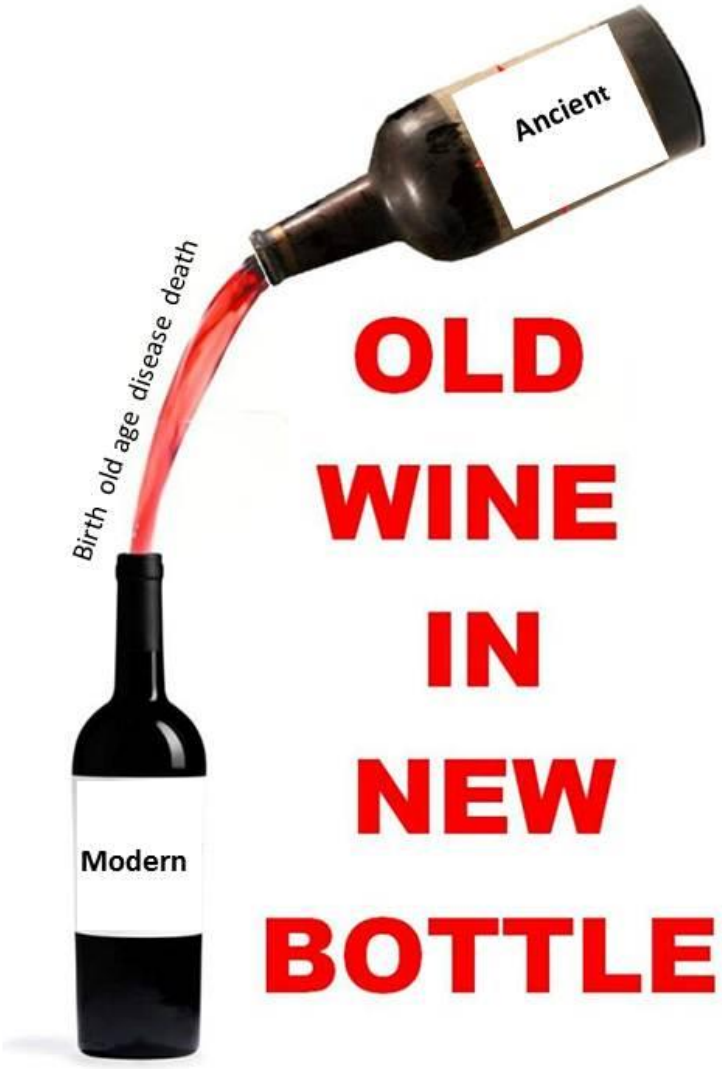
Additionally, "Upon request, the laboratory shall make its ***estimates of measurement uncertainty available to laboratory users***"

MU ESTIMATES : WHAT IS THE VALUE ?

- Indicate that ***multiple value***s are possible for a given measurement;
- Provide evidence that the term ***"true value"*** of a quantity is a ***theoretical concept***;
- Quantify the quality of a result relative to its ***suitability for use*** in making ***medical decisions***;
- Assume that known medically significant ***bias is eliminated***
- Assist in identifying ***technical steps*** to reduce MU

MEASUREMENT UNCERTAINTY and CLINICAL-LABORATORY COMMUNICATION

The admission of ***uncertainty*** forms the starting point for a ***more open conversation*** between laboratory professionals and clinicians (and patients too)



OLD WINE IN NEW BOTTLE

ELSEVIER

Clinica Chimica Acta 346 (2004) 25–35

www.elsevier.com/locate/clinchim

What information on quality specifications should be communicated to clinicians, and how?

Mario Plebani*

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Received 18 December 2003; accepted 19 March 2004

Conclusions: A proposal has been made to improve the way laboratory results are communicated to clinicians, with practical information derived from quality specifications. By providing clinicians with information on quality characteristics and the degree of uncertainty, a more objective interpretation of laboratory data may be possible, and data may be more appropriately utilized for diagnosis and monitoring.

PADOVA'S LABORATORY REPORTS

REGIONE DEL VENETO
AZIENDA OSPEDALIERA - UNIVERSITA' - AULSS6 EUGANEA
DIPARTIMENTO STRUTTURALE MEDICINA DI LABORATORIO
U.O.C. Medicina di Laboratorio
(SGQ ISO 9001:2008)
Direttore: Prof. Mario Plebani

TE

P-POTASSIO errore totale ≤5%	***3,7***	mmol/L	3,4 - 4,5	3,6	10/10/17
P-BILIRUBINA TOTALE errore totale ≤18,5%	***16,9***	umol/L	1,7 - 17,0		
P-BILIRUBINA CONIUGATA	**** 11,9***	umol/L	0,0 - 5,1		
P-BILIRUBINA NON CONIUGATA	***5,0***	umol/L	3,4 - 13,7		

MARCATORI DI MALATTIA

S-CEA Variazione (%) *vs* precedente	**** 51,3*** ***-26,8***	ug/L %	0,0 - 5,0 (significativo > 40,6%)	70,1	05/09/17
S-CA 19-9	***29,6***	kU/L	0,0 - 37,0	64,4	05/09/17

RCV

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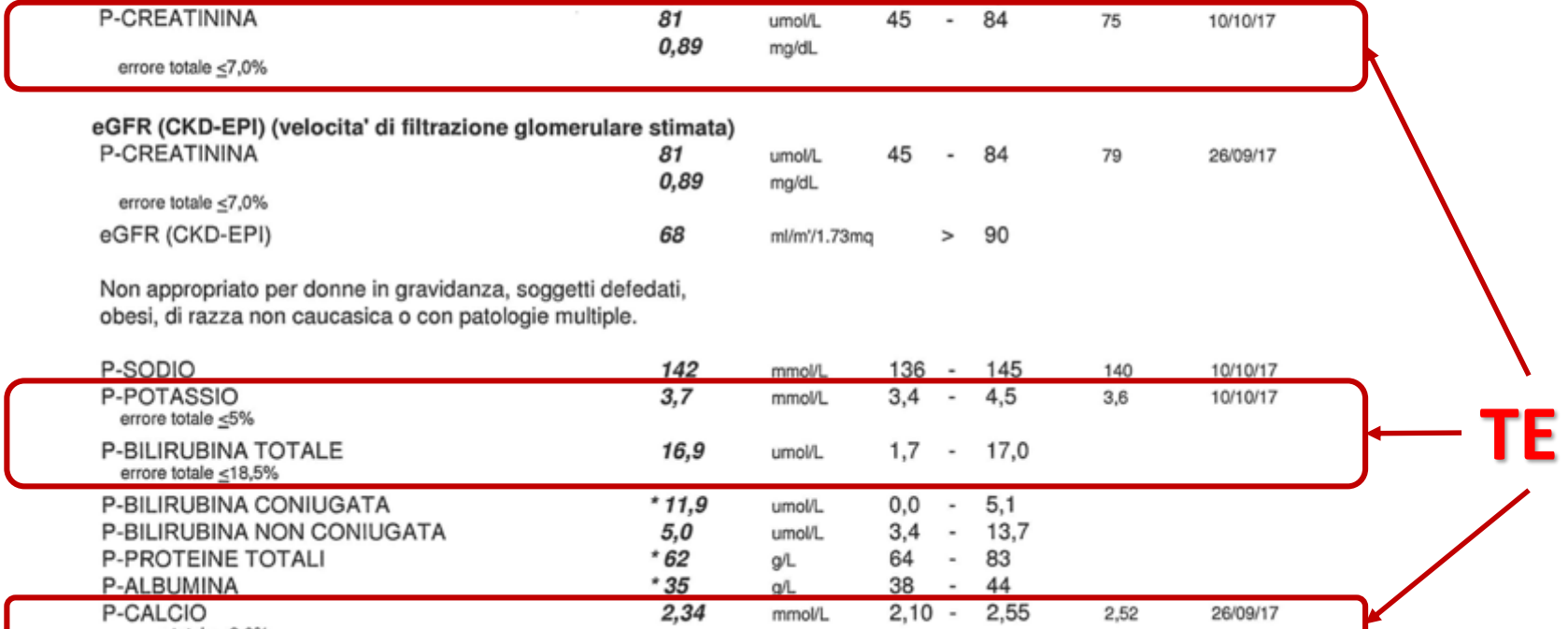
REGIONE DEL VENETO ULSS6 EUGANEA

Costituente	Risultato	Unita'	Int. di Riferimento	Ris. Prec.	
COSTITUENTI BIOCHIMICI					
P-GLUCOSIO	* 5,8	mmol/L	3,7 - 5,6	5,1	10/10/17
	104	mg/dL			
	alterata a digiuno:		5,7 - 6,9		
	gravidanza:		3,7 - 5,1		
P-UREA	5,80	mmol/L	2,50 - 7,50		
P-CREATININA	81	umol/L	45 - 84	75	10/10/17
	0,89	mg/dL			
errore totale ≤7,0%					
eGFR (CKD-EPI) (velocita' di filtrazione glomerulare stimata)					
P-CREATININA	81	umol/L	45 - 84	79	26/09/17
	0,89	mg/dL			
errore totale ≤7,0%					
eGFR (CKD-EPI)	68	ml/m'/1.73mq	> 90		
Non appropriato per donne in gravidanza, soggetti defedati, obesi, di razza non caucasica o con patologie multiple.					
P-SODIO	142	mmol/L	136 - 145	140	10/10/17
P-POTASSIO	3,7	mmol/L	3,4 - 4,5	3,6	10/10/17
errore totale ≤5%					
P-BILIRUBINA TOTALE	16,9	umol/L	1,7 - 17,0		
errore totale ≤18,5%					
P-BILIRUBINA CONIUGATA	* 11,9	umol/L	0,0 - 5,1		
P-BILIRUBINA NON CONIUGATA	5,0	umol/L	3,4 - 13,7		
P-PROTEINE TOTALI	* 62	g/L	64 - 83		
P-ALBUMINA	* 35	g/L	38 - 44		
P-CALCIO	2,34	mmol/L	2,10 - 2,55	2,52	26/09/17
errore totale ≤3,0%					
P-MAGNESIO	* 0,64	mmol/L	0,70 - 1,05		
P-AST	25	U/L	10 - 35	25	10/10/17



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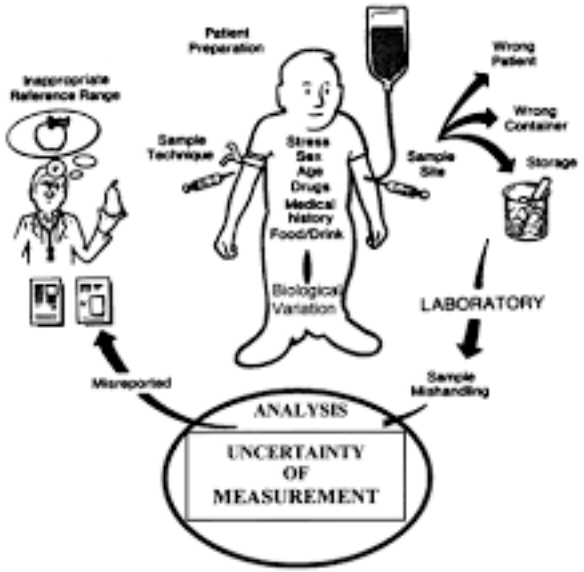
P-ALT	***15***	U/L	7 - 35	13	10/10/17
P-gGT errore totale ≤6%	**** 87***	U/L	3 - 45		
P-ALP	***115***	U/L	53 - 141		
P-LAD	**** 129***	U/L	135 - 214		

MARCATORI DI MALATTIA

S-CEA	**** 51,3***	ug/L	0,0 - 5,0	70,1	05/09/17
Variazione (%) *vs* precedente	***-26,8***	%	(significativo > 40,6%)		
S-CA 19-9	***29,6***	kU/L	0,0 - 37,0	64,4	05/09/17

RCV

Why measurement uncertainty should be adopted in Medical Laboratories ?



MU ESTIMATES
WHAT IS THE VALUE ?

- To be used to determine if medically ***allowable analytical performance specifications*** should be/are really ***achieved*** (in routinary practice)
- To support ***interpretation of patient results, particularly*** close to medical decision limits

Measurement Uncertainty (MU) Aims

(within the laboratory)

To provide evidence of the compliance with analytical performance characteristics

(To users)

To provide objective information for an appropriate interpretation of laboratory results

Plebani M Clin. Biochem. 2018

MEASUREMENT UNCERTAINT (MU)

WITHIN THE LABORATORY

- **TO COMPLY:**
  with established analytical performance characteristics
- **TO MONITOR:**
  Imprecison (IQc) and bias (EQAs)
- **TO IDENTIFY:**
  Sources of uncertainty

CLINICAL-LABORATORY INTERFACE

- **Objective information for appropriate interpretation/ utilization of laboratory results**

- **Benchmark (performance characteristics)**
- **Driver for harmonization**
- **Driver for comparability and interchangeability of laboratory results**

What is measurement uncertainty ?

What is measurement uncertainty ?

*A "non-negative parameter **characterizing the dispersion of the quantity values being attributed to a measurand**, based on the information used "*

$$\text{result} \pm U$$

Measurement result

Non negative Dispersion parameter characterizing the dispersion of X

JCGM 200:2008. International vocabulary of metrology – Basic and general concepts and associated terms (VIM), 3rd edition 2008

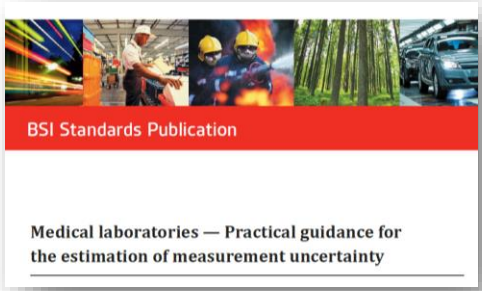
UNCERTAINTY IN LABORATORY MEDICINE

Uncertainty is a property of a measurement result which expresses ***lack of knowledge*** of the true value of the result and incorporates the factors known to influence it.

Uncertainty, therefore, is a ***quantification of doubt*** about the measurement result as is caused by the interplay of errors which create ***dispersion around the estimated value*** of the measurand: the smaller the dispersion, the smaller the uncertainty.

Main guidelines available for estimating measurement uncertainty for medical laboratories

ISO/TS 20914:2019 (first edition 7-2019)



- **1980** — INC-1
- **1993** — GUM 1st edition
- **1995** — GUM 2nd print
- **2004** — EA4-16 (Cofrac)
- **2008** — GUM 3rd print
- **2012** — Nordtest TR 537 ed. 3.1; Eurachem CITAC Guide CG 4, 2012; CLSI EP29-A
- **2014** — CAP 15189 program

Approaches to measurement uncertainty estimation

GUM – JCGM 200:2008

Measurement uncertainty should be calculated by **Type A and Type B uncertainties.**

Type A evaluations include any statistical analysis of a series of observation; Type B evaluations include any methods for evaluating uncertainty from distribution of error "a priori" known.

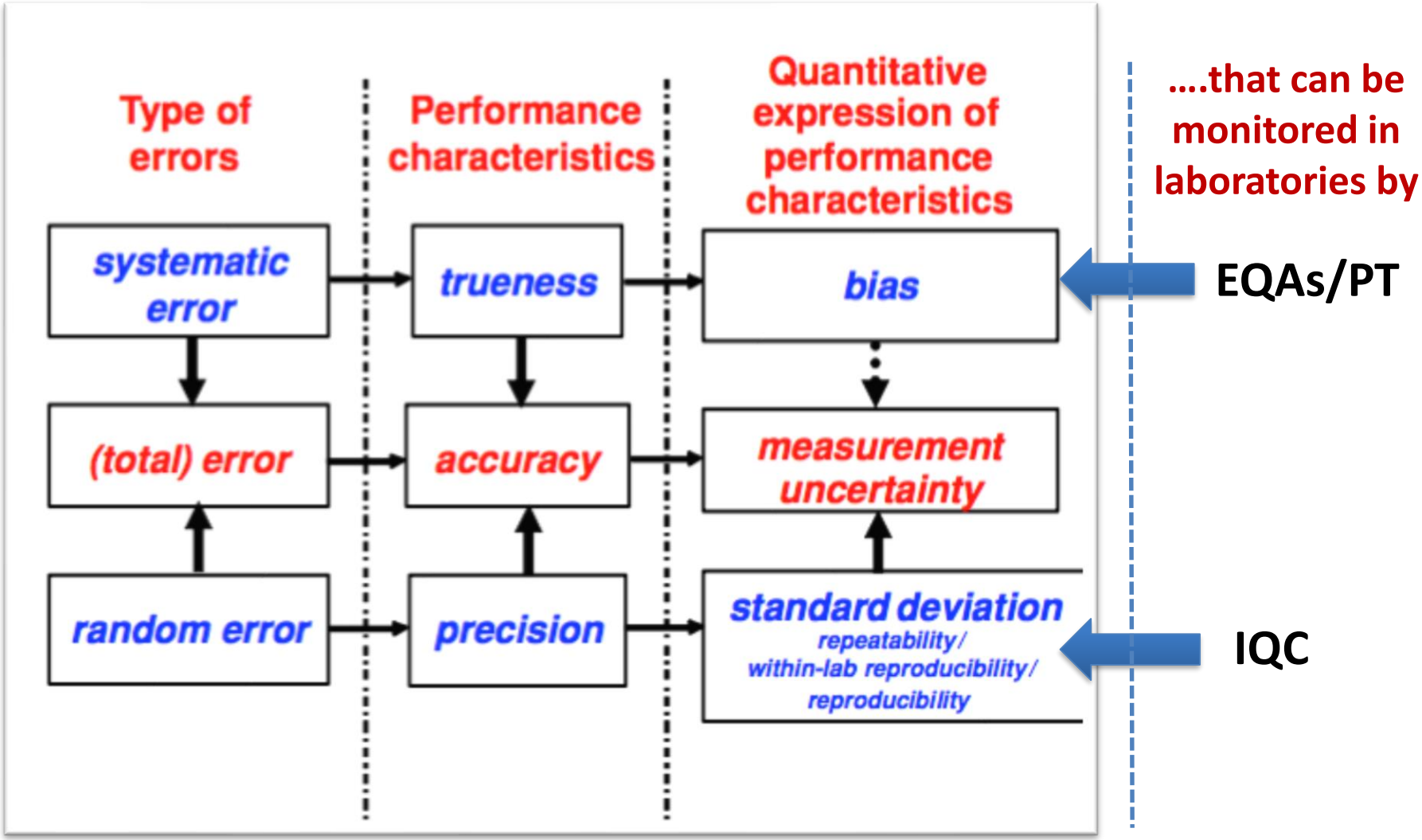
CLSI EP29 - 2012

Measurement uncertainty should be calculated either by **Top Down or Bottom up approaches**.

NORDTest – 2012

Proposed an approach based on **precision and systematic errors** that may be estimated by IQC and EQAs results.

STATE OF THE ART



Modified from Menditto et al. Accred Qual Assur 2007; 12:45.

Sources of uncertainty can be combined

- Uncertainty of measurement comprises, in general, many components, each one definable as **standard uncertainty (u).**
- Different standard uncertainty may be finally combined into quantities called **combined uncertainty (u_c)**
- **Combined uncertainty,** should be expanded to the **expanded uncertainty, with a given confidence (usually approximately 95%)**

Many possible sources of uncertainty….

a) *incomplete definition of the measurand;*
b) *imperfect realization of the definition of the measurand;*
c) *nonrepresentative sampling — the sample measured may not represent the defined measurand;*
d) *inadequate knowledge of the effects of environmental conditions on the measurement or imperfect measurement of environmental conditions;*
e) *personal bias in reading analogue instruments;*
f) *finite instrument resolution or discrimination threshold;*
g) *inexact values of measurement standards and reference materials;*
h) *inexact values of constants and other parameters obtained from external sources and used in the data-reduction algorithm;*
i) *approximations and assumptions incorporated in the measurement method and procedure;*

JCGM 100:2008. Guide to the expression of uncertainty in measurement. 2008.

July 2019

PD ISO/TS 20914:2019

BSI Standards Publication

Medical laboratories — Practical guidance for the estimation of measurement uncertainty

Document prepared by Technical Committee ISO/TC 212, Clinical laboratory testing and in vitro diagnostic test systems.

MU AND FIT-FOR-PURPOSE OF TEST RESULTS

“ a **“one size fits all” calculation of MU is inappropriate**; rather MU should be calculated depending on how the “true” value is obtained and applied depending on the type of comparison required for correct result interpretation.

Example scenarios of the components of MU calculation are given ranging from the simplest comparison of a previous result from the same patient (e.g. serial troponin measurements within a short time period on the same analyzer within one calibration), **to repeat measurements over multiple calibrations**, to the interpretation of results against a population reference interval or a clinical decision limit ”

Tate J and Plebani M. CCLM 2016; 54:1277

MU AND FIT-FOR-PURPOSE OF TEST RESULTS

Test Purposes and Uncertainty: components to be included

Test purpose	Examples	Components to be included in measurement uncertainty
Test results are primarily used for **monitoring** patients over time	**e.g.** tumour markers, immunosuppressive drugs.	**Imprecision only** Jones GR. CCLM 2016; 54:1303 Tate J and Plebani M. CCLM 2016; 54:1277
Test result if used in **comparison with a reference interval** either established in the same laboratory or verified by the laboratory by appropriated procedures	**e.g.** hormones	**Imprecision only** Jones GR. CCLM 2016; 54:1303
Test result is usually **compared with a clinical decision point**	**e.g.** glucose, ions	**Imprecision, bias and bias uncertainty** Jones GR. CCLM 2016; 54:1303

Padoan A. Clin Biochem. 2018 Jul;57:41-47

July 2019

PD ISO/TS 20914:2019

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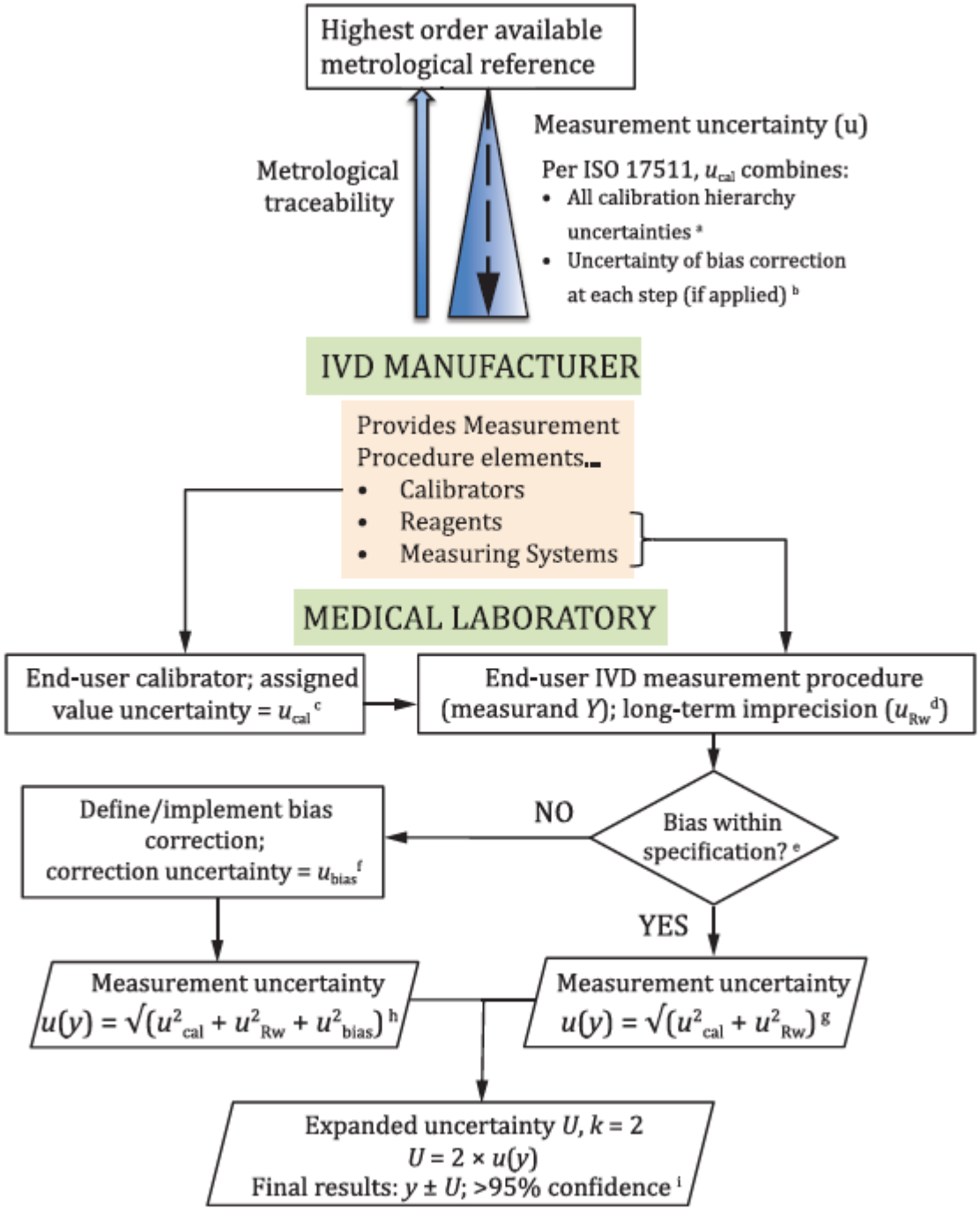
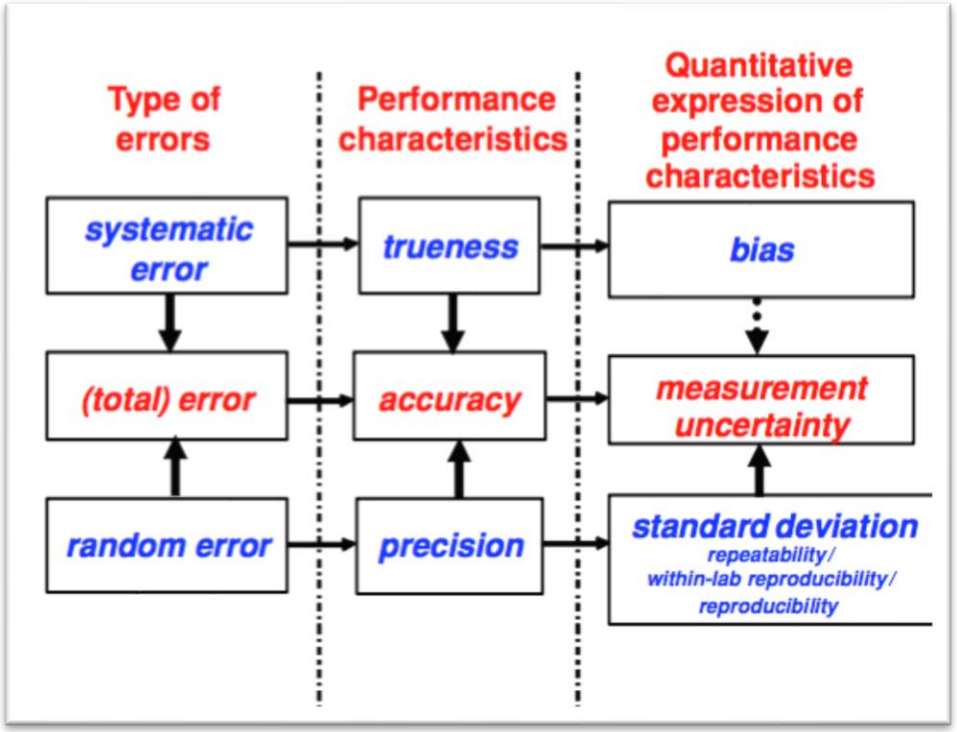
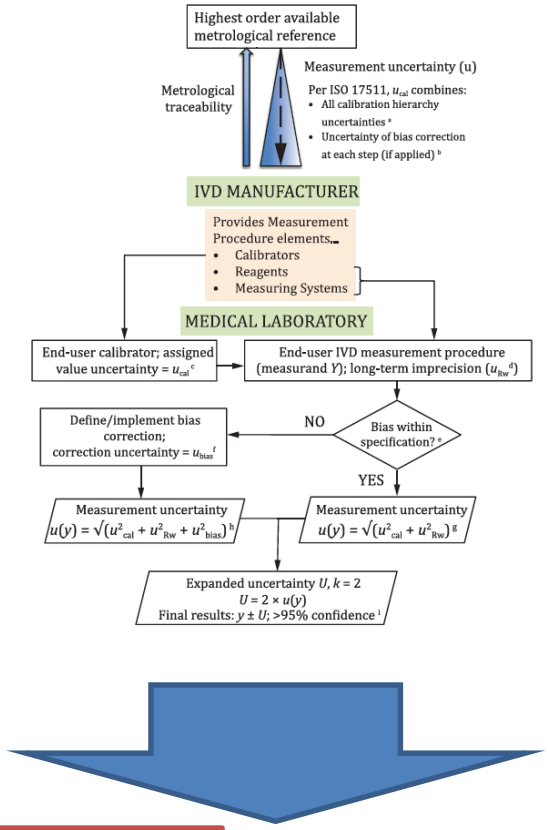
ISO20914:2019 flow chart



ISO 20914:2019
The Change of View





Long term precision

Uncertainty of calibrator

ISO 20914:2019 MU Calculation

1) Absence of medically significant bias and lack of calibration uncertainty

$$u(y) = \sqrt{(u_{RW}^2)}$$

2) Absence of medically significant bias and data on calibration uncertainty present

$$u(y) = \sqrt{(u_{cal}^2 + u_{RW}^2)}$$

3) Presence of medically significant bias, correction for bias uncertainty, and data on calibration uncertainty present

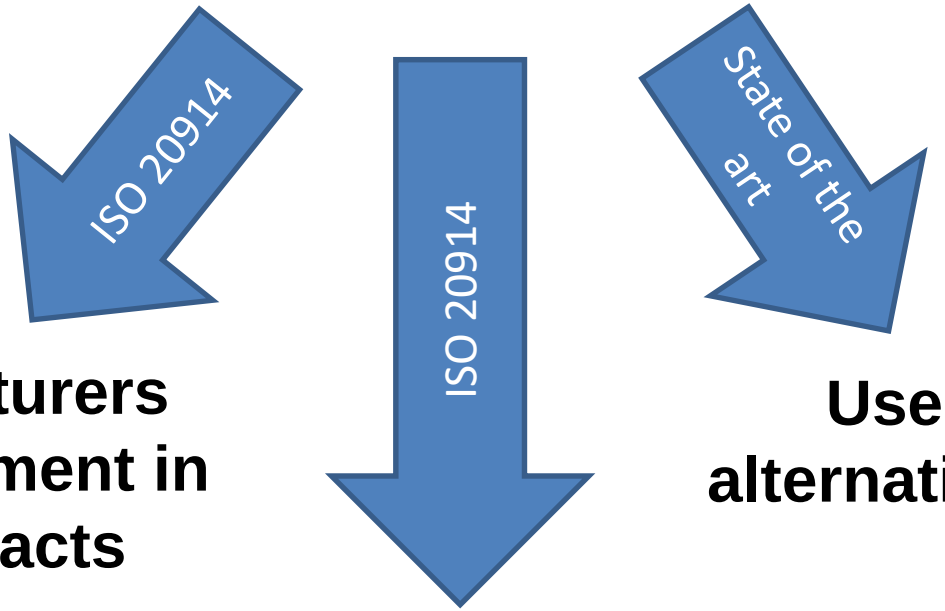
$$u(y) = \sqrt{\left(u_{bias}^2 + u_{cal}^2 + u_{RW}^2\right)}$$

THE MOST SIGNIFICANT UNCERTAINTY CONTRIBUTIONS TO OVERALL MU

- ***Long-term imprecision*** data obtained for IQC materials for a ***period sufficient*** to include all changes to measuring conditions (U_{RW})
- ***Uncertainty of end-user calibrator*** values (U_{cal})- obtainable from the manufacturer or established by a laboratory that develops its own measuring system

Uncertainty of end-user calibrator

Because only few manufacturers provide uncertainty of their calibrators



Ask manufacturers for this requirement in supply contracts

Use intermediate imprecision only

Use pragmatic, alternative approaches

DE GRUYTER

Clin Chem Lab Med 2017; aop

Andrea Padoan*, Giorgia Antonelli, Ada Aita, Laura Sciacovelli and Mario Plebani

An approach for estimating measurement uncertainty in medical laboratories using data from long-term quality control and external quality assessment schemes

DOI 10.1515/cclm-2016-0896
Received October 6, 2016; accepted January 18, 2017

Abstract

Background: The present study was prompted by the ISO 15189 requirements that medical laboratories should estimate measurement uncertainty (MU).

Methods: The method used to estimate MU included the: a) identification of quantitative tests, b) classification of tests in relation to their clinical purpose, and c) identification of criteria to estimate the different MU components. Imprecision was estimated using long-term internal quality control (IQC) results of the year 2016, while external quality assessment schemes (EQAs) results obtained readily be implemented in medical laboratories as a useful tool in monitoring the analytical quality of test results since they are calculated using a combination of both the long-term imprecision IQC results and bias, on the basis of EQAs results.

Keywords: external quality assessment schemes (EQAs); internal quality controls (IQC); ISO 15189; measurement procedures (MPs); measurement uncertainty (MU); medical laboratory accreditation.

Introduction

FIT-FOR-PURPOSE OF TESTS

The different test purposes were evaluated and measurement uncertainty values were estimated differently on the fit for test purposes (mainly used for diagnosis or for patients' monitoring)

The purpose is mainly monitoring: only imprecision was used for calculating measurement uncertainty

Other purposes (e.g. diagnosis): both imprecision and bias were used for calculating measurement uncertainty

After ISO 20914:2019 …

DE GRUYTER

Clin Chem Lab Med 2017; aop

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Introduction

PD IS

BSI Standards Publication

BS EN ISO 15189:2012
Incorporating corrigendum October 2014

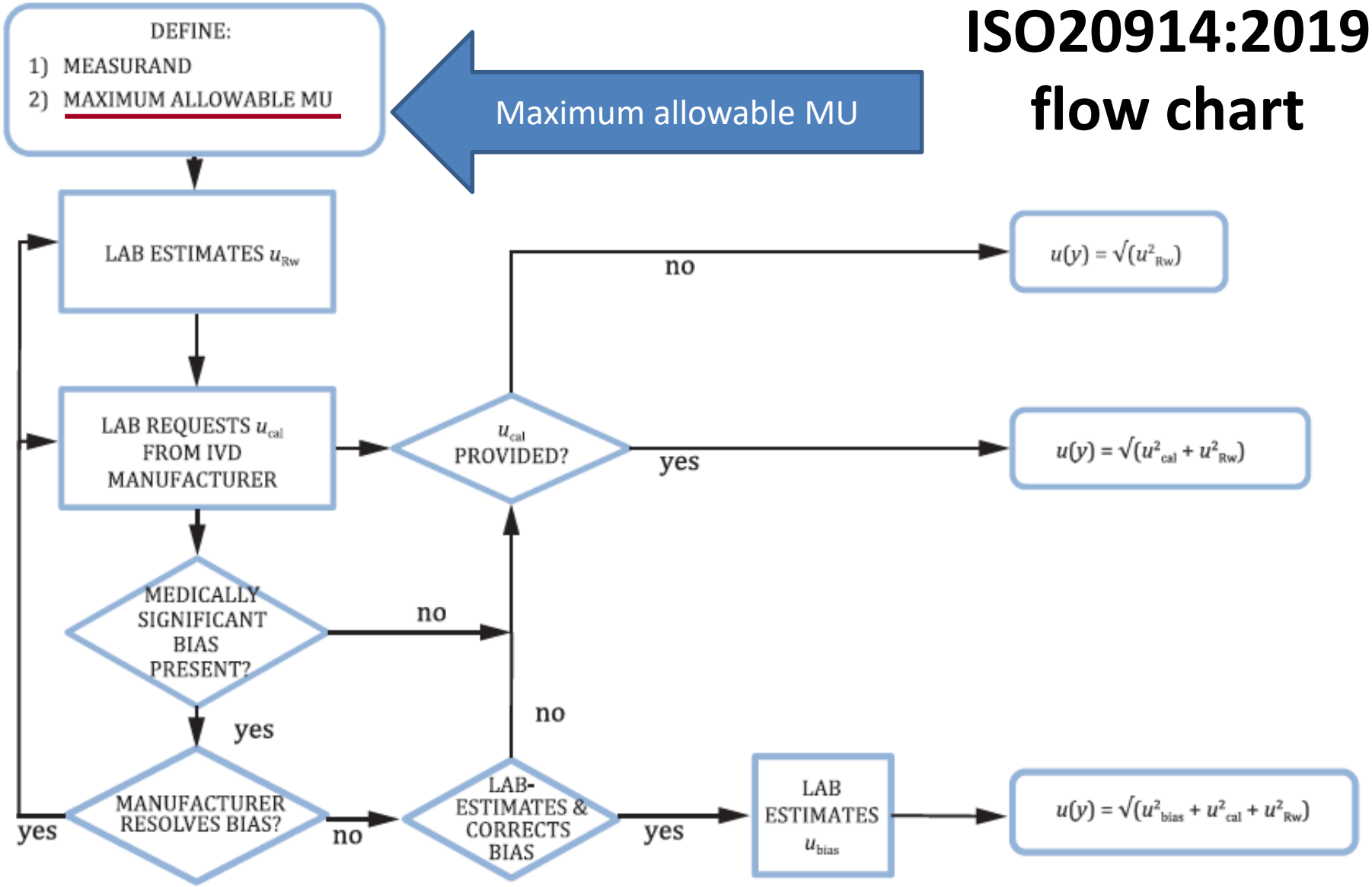
BSI Standards Publication

Medical laboratories — Requirements for quality and competence (ISO 15189:2012)

Medical laboratories — Practical guidance for the estimation of measurement uncertainty

A new practical approach should be evaluated …

ISO20914:2019 flow chart



MAXIMUM ALLOWABLE MU

- The magnitude of MU should be ***suitable for a result to be used in a medical decision*** and ideally as small as technically possible
- ….estimating the expanded uncertainty of the results produced is of ***very limited value unless it can be compared*** with an upper limit of allowable expanded uncertainty based on the quality of ***results required for medical use***

ISO/TS 2914: 2019

MAXIMUM ALLOWABLE MU

Such limits should be based on models defined by the 2014 EFLM Consensus Conference including ***clinical outcomes***, a selected proportion of ***biological variation***, or, when information derived from the first two models are lacking, ***state-of-the-art*** of the measurement performance

ISO/TS 2914: 2019

Should MU be communicated and how in Laboratory Reports?

MEASUREMENT UNCERTAINTY (MU)

AIMS OF MU

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

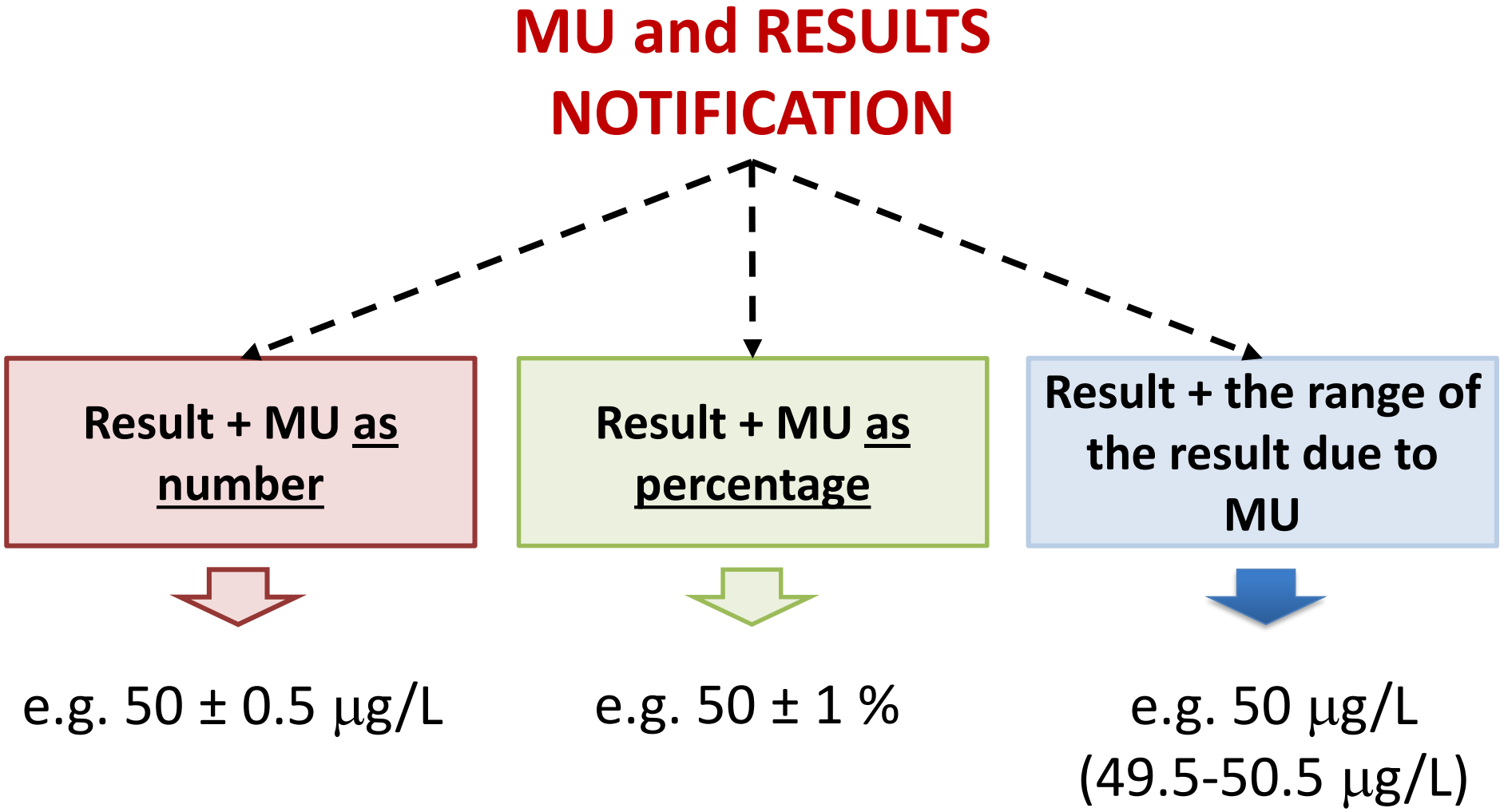
What information on measurement uncertainty should be communicated to clinicians, and how?

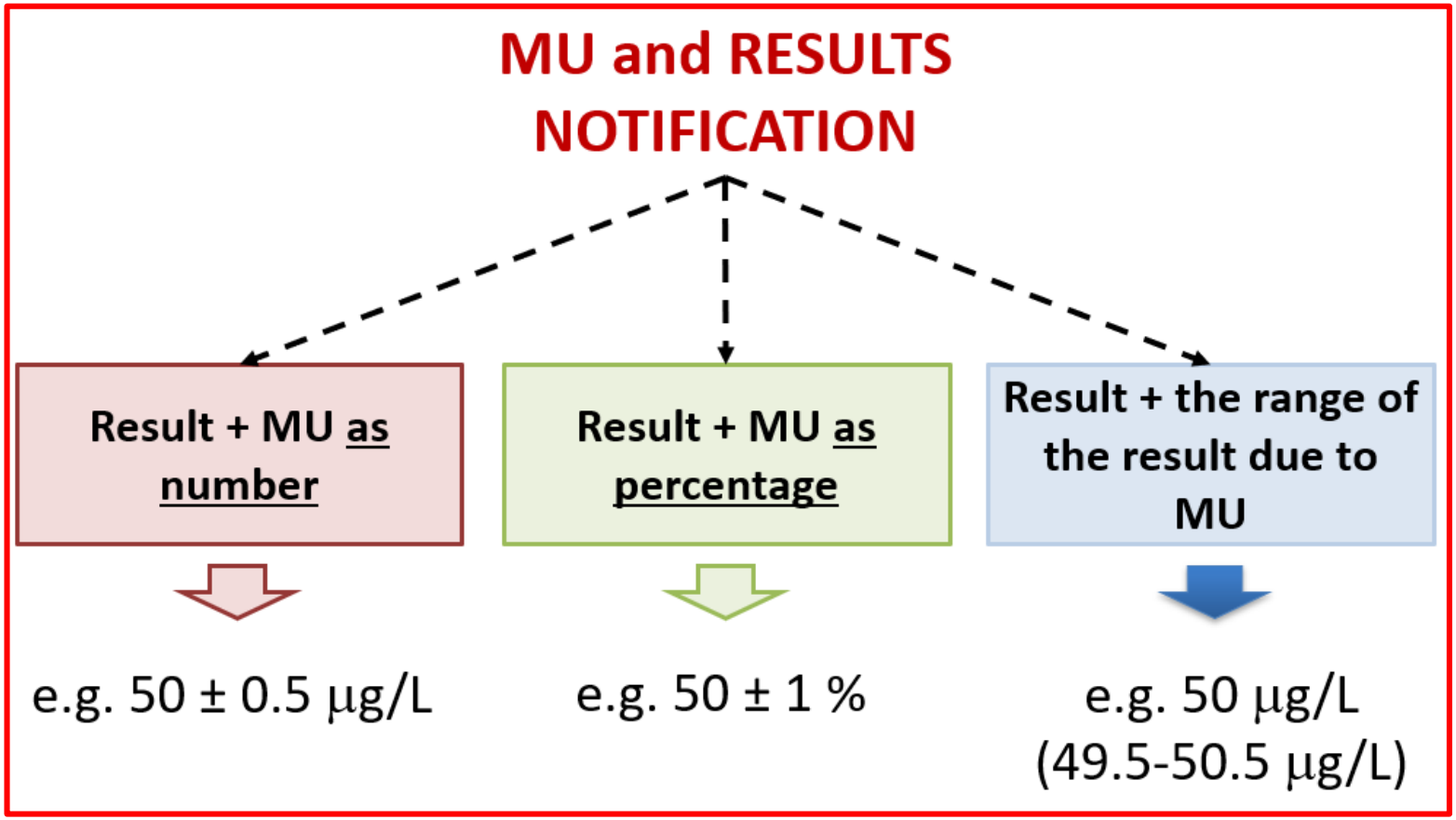
Plebani Mario*, Sciacovelli Laura, Bernardi Daniela, Aita Ada, Antonelli Giorgia, Padoan Andrea

Department of Laboratory Medicine, University-Hospital of Padova, Via Giustiniani 2, 35128 Padova, Italy

- Monitoring imprecision (IQC) and bias (EQAs)
- Aiding in the identification of sources of uncertainty

RESULTS NOTIFICATION





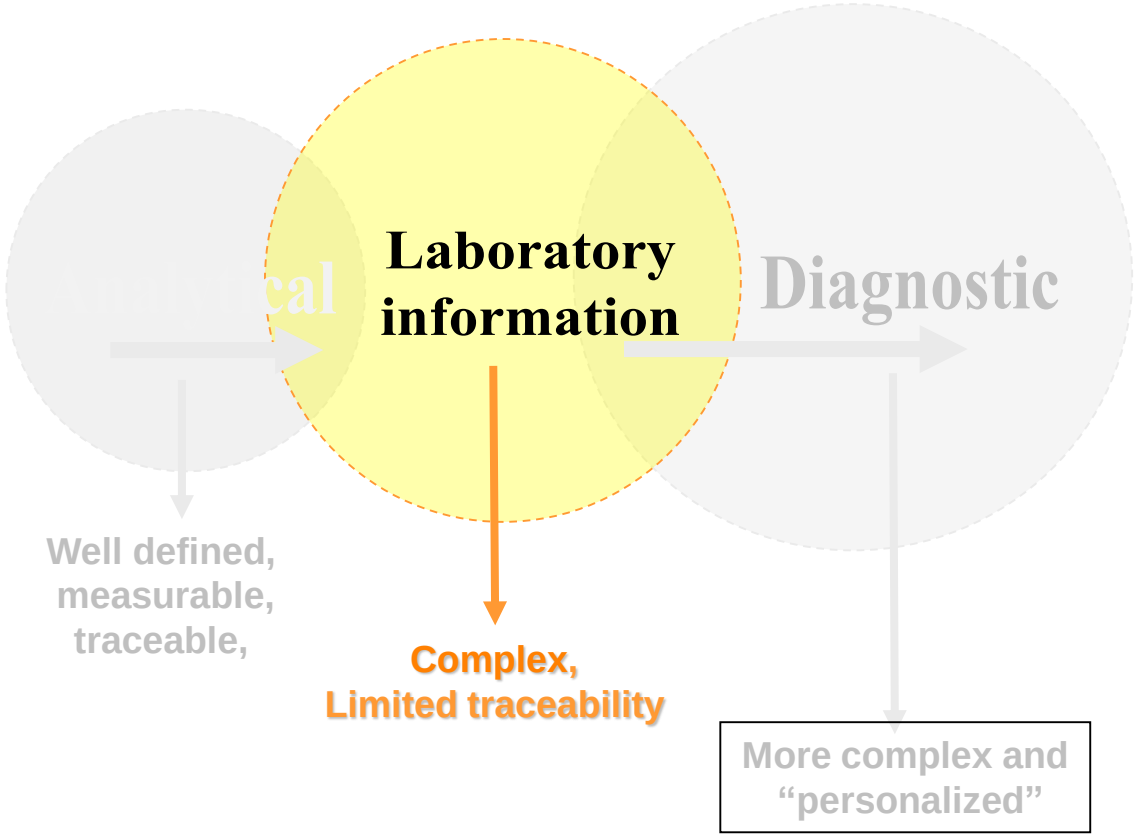
- MU should be reported considering the measurand concentration (different concentration, different MU)
- Reporting the result + range facilitate the clinician interpretation

MU and LABORATORY REPORTS

- Including ***information*** on the ***reliability of results*** in the laboratory report may lead to a more careful evaluation of their effective value in diagnosing and monitoring diseases.
- Although interest in ***evidence-based medicine*** has increased in recent years, evidence-based strategies have been inconsistently adopted in patient care.

Plebani M. Clin Chem Lab Med 2007

UNCERTAINTY



UNCERTAINTY OF LABORATORY INFORMATION

- ***Request appropriateness***
- ***Quality of biological samples*** **(Pre-pre-analytical phase)**
- ***Appropriate intepretative criteria*** **(measurement units, reference range, decision limits, refernce change value)**
- ***Post-post-analytical quality*** **(timeliness, right interpretation/utilization of laboratory information, outcomes)**

INTERFERING SUBSTANCES and MU

Sources of uncertainty may arise from ***interfering substances*** that modify the ***interaction*** of the analyte with the measuring system and/or the ***signal*** generated by the measurement process.

Examples include ***patient antibodies*** to the analyte or reagent, spectrofotometric ***interference by free haemoglobin***, or ***cross-reactivity*** of structurally related molecules

These ***pre-measurement sources of uncertainty*** are generally individual sample-specific and ***not included*** in ***the estimation of MU*** for typical human samples.

ISO/TS 2914: 2019

COMBINED UNCERTAINTY AND PRE-ANALYTICAL ERRORS

*"However, it seems quite **difficult to incorporate the pre- and post-analytical uncertainty into an MU calculation**. The alternative way is to identify and continuously reduce the risk of errors in the extra-analytical phases through a risk management process that, according to ISO 15189, takes into consideration all steps of the cycle, namely the steps that are more vulnerable to error and risk of errors"*

Tate J and Plebani M. CCLM 2016; 54:1277

Uncertainty and pre-analytical factors

"However, some laboratorians believe that searching for ***pre-analytical quality***, e.g. by rejecting haemolysed samples, should delay/damage patients care. If so, pre-analytical uncertainty should be considered and notified to clinicians.

But which ***degree of uncertainty*** should be "permitted" and how should it be "calculated" ? This is clearly a patient safety issue".

DE GRUYTER

Clin Chem Lab Med 2019; aop

Opinion Paper

Andrea Padoan*, Laura Sciacovelli, Rui Zhou and Mario Plebani

Extra-analytical sources of uncertainty: which ones really matter?

Abstract: Since the endorsement by ISO15189:2012 of measurement uncertainty (MU) for the estimation of error in measurement procedures, the debate has been ongoing with questions concerning which method should be used for estimating MU and the benefits of using MU over other error methods. However, only limited attention has been given to extra-analytical sources of uncertainty and, currently, a clear standpoint is still missing. This opinion paper aims to evaluate whether extra-analytical variables could be included in MU. Considering coagulation tests as an example, the possible sources of preanalytical variations are evaluated by using a fishbone diagram. After excluding preanalytical errors, additional sources of uncertainty are divided into amenable to standardization/harmonization and/or possible random sources, which are not standardizable nor harmonizable. Finally, sources of uncertainty are evaluated for a possible inclusion into MU. In addition, postanalytical uncertainty is discussed, particularly considering the laboratory results calculated through a mathematical equation, derived from one or more quantities affected by their specific uncertainty.

Extra-analytical variability

Errors

Extra-analytical errors should not be considered as sources of uncertainty

Extra-analytical Sources of uncertainty

Amenable to standardization/harmonization

Reduce variability of these sources by appropriate standardization approaces

Random occurring

If the magnitude of effect is clearly estimable, it can be included in MU estimation

Table 1: Preanalytical sources of variation for laboratory tests.

Preanalytical sources of variations			
Patients	**Blood collection**	**Sample handling**	**Analytical interferences**
Standardization/harmonization possible – Posture during venipuncture – Fasting – Daily and age-related circadian rhythms[a] – Drugs (e.g. antibiotics, anticoagulants, hormonal contraceptives, etc.)[b] – Pathophysiological alterations (thrombosis, autoimmune disease, etc.)[b] – Elective cases such as pregnancy, breastfeeding and menstrual cycle – Dietary factors or food supplements known to cause an effect on test result (e.g. biotin) – Physical exercise	– Between-operators venipuncture variations (e.g. tourniquets usage, tube order, etc.)	– Centrifugation conditions (time, force and temperature) – Temperature of sample transportation – Time of sample transportation	– Hemolyzed samples – Lipemic samples – Clotted samples – Icteric samples
Occurring random or standardization/harmonization not possible – Circadian seasonal rhythms – Dietary factor or food supplements not known to cause an effect on test result	– Between-part and between-lot variations in blood collection tubes (such as, e.g. aging of blood collection device variations) – Between operator (e.g. individual choice of the type of the blood collection device based on the specific patients)	– Pneumatic tube transportation	– Possible heterophile antibodies interferences[c]

Sources are divided in (a) amenable to standardization/harmonization or (b) random occurring, which are not standardizable/not harmonizable. [a]Standardizable/harmonizable by using different reference intervals. [b]Determinable by questionnaire. [c]They may affect some specialized hemostasis assays.

HOW SHOULD UNCERTAINTY OF LABORATORY INFORMATION BE REDUCED/LIMITED?

UNCERTAINTY of LABORATORY INFORMATION

- Request appropriateness
- Quality of biological samples (Pre-pre-analytical phase)
- Appropriate intepretative criteria (measurement units, reference range, decision limits, refernce change value)
- Post-post-analytical quality (timeliness, right interpretation/utilization of laboratory information, outcomes)

Standardization

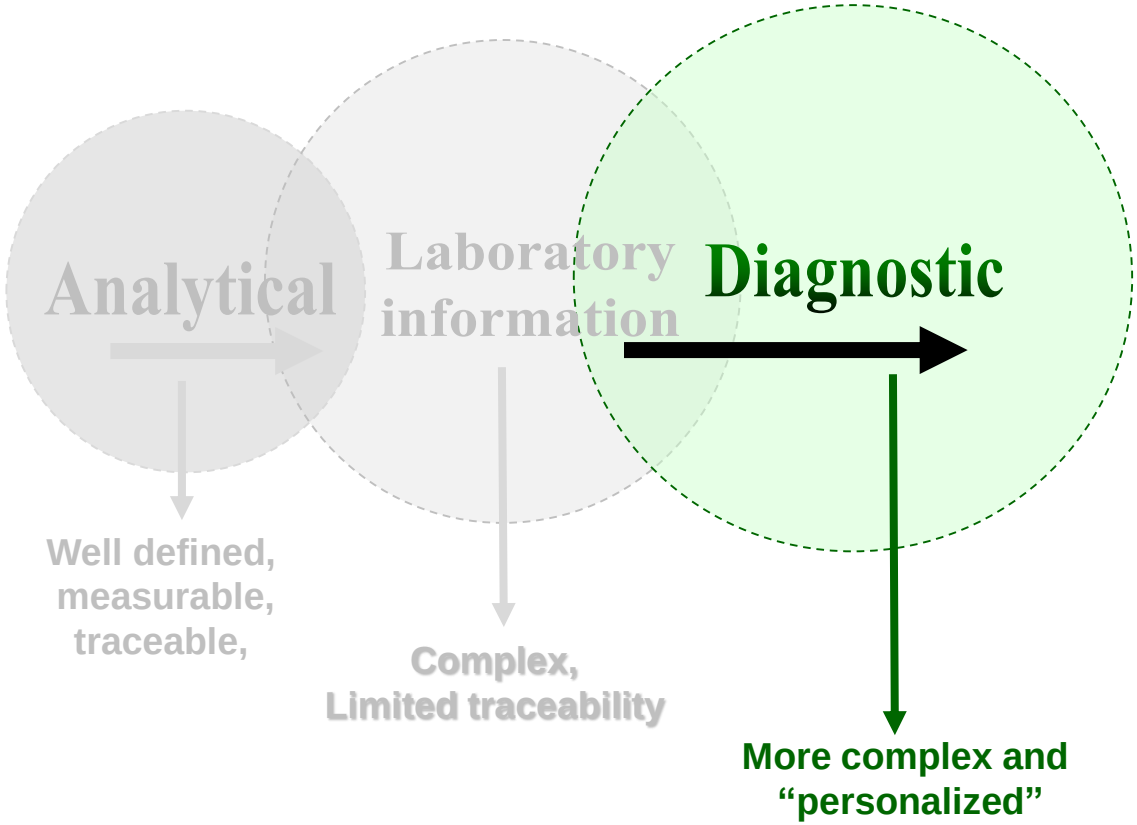
Harmonization

Guidelines

Clinicians cooperation

Clinical decision support

UNCERTAINTY



ONLY UNCERTAINTY IS A SURE THING

The reality is that doctors continually have to ***make decisions*** on the basis of ***imperfect data*** and limited knowledge, which leads to ***diagnostic uncertainty***, coupled with the uncertainty that arises from unpredictable patient response to treatment and from health care outcomes that are far from binary.

Simpkin AL, Schwartzstein RM. N Engl J Med 2016

DIAGNOSTIC UNCERTAINTY

"…. laboratory uncertainty is a small part in the whole clinical reasoning that leads to decision-making and includes past experience of physicians, the ***pre-test probability*** of a disease or the disease prevalence, the uncertainty originating ***from the measuring procedure*** and from the interpretation of the results in view of the patient's clinical parameters or comorbidities and in differential diagnosis".

Padoan et al. Clin. Chem. Lab. Med. (2019).

REDUCING DIAGNOSTIC UNCERTAINTY

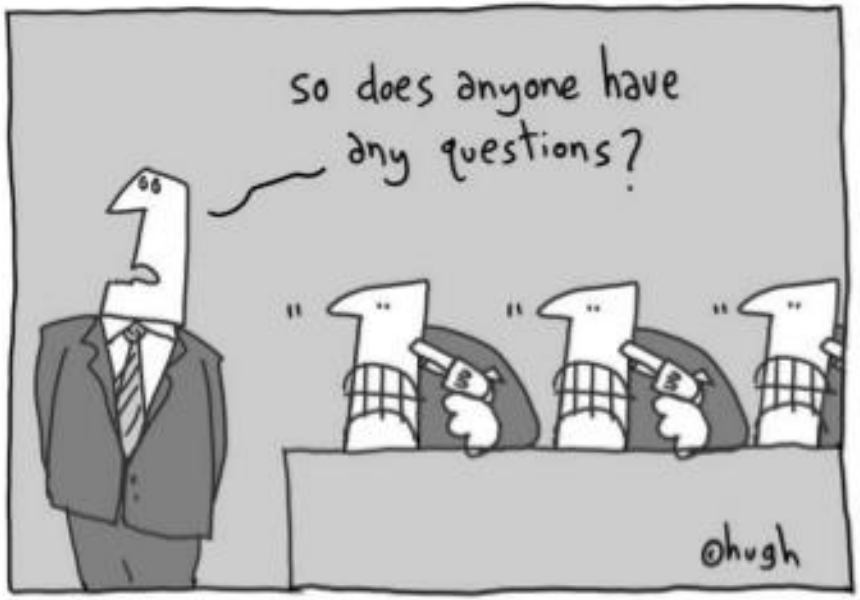
Ironically, as ***tests have become more precise*** and "precision medicine" has become major pre-occupation, there is growing awareness and appreciation of the ***pervasiveness of uncertainty*** in medicine.

……more ***intelligent test selection***, ***timing, and interpretation***, and using a more balanced understanding of their benefits, harms, costs, and limitations.

Schiff GD et al Ann Int Med 2018

Diagnostic uncertainty

Thank you for your attention!



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