AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

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

Mario Plebani

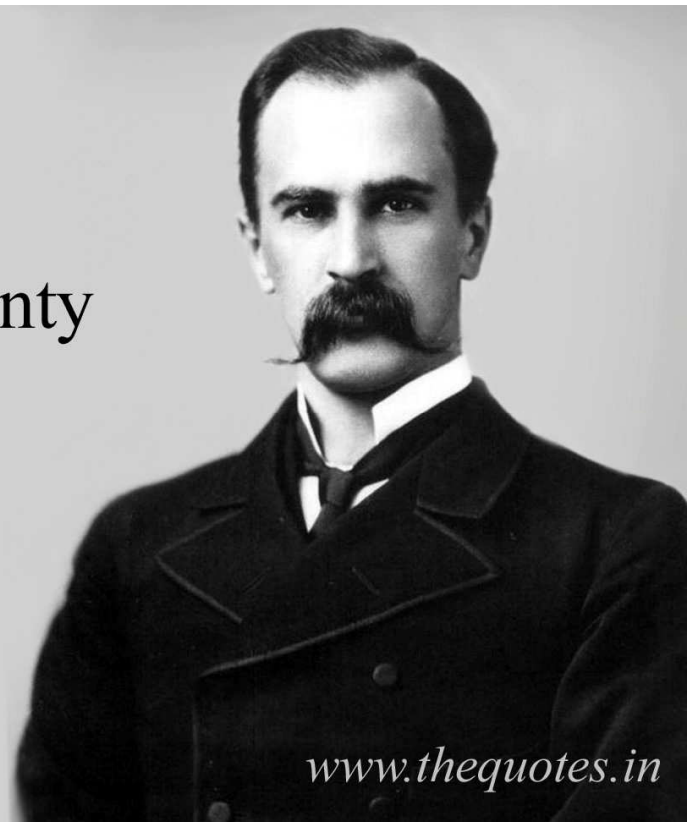
OUTLINE OF TALK

- ***Uncertainty in medicine*** and shared decision making
- ***Measurement uncertainty*** in laboratory medicine (MU)
- ***What information*** on MU should be ***communicated*** to clinicians?
- ***How*** should MU be communicated to clinicians ?

CERTAINTY IS AN ILLUSION

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

William Osler



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

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 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.

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

MEASUREMENT UNCERTAINTY (MU)

AIMS OF MU

Within the laboratory

To provide evidence of the compliance with analytical performance characteristics by:

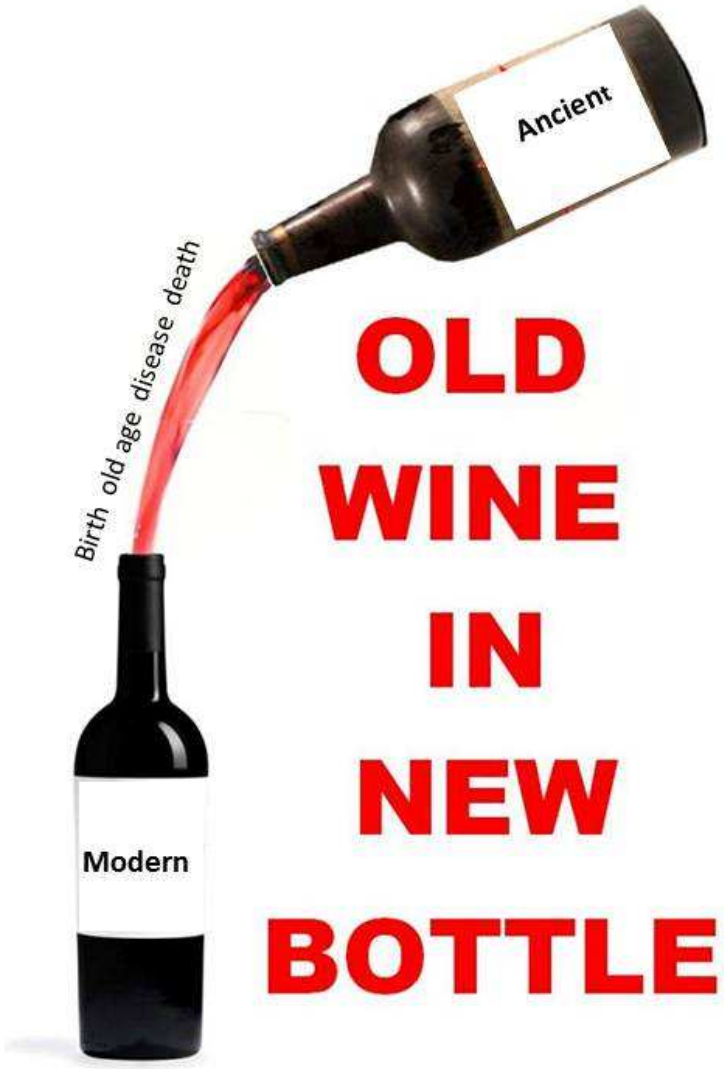
- Setting appropriate quality specifications
- Monitoring imprecision (IQC) and bias (EQAs)
- Aiding in the identification of sources of uncertainty

To users

To provide objective information for an appropriate interpretation of laboratory results with the aim of improving patient care and safety

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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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/m²/1.73mq	> 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

TE

REGIONE DEL VENETO

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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

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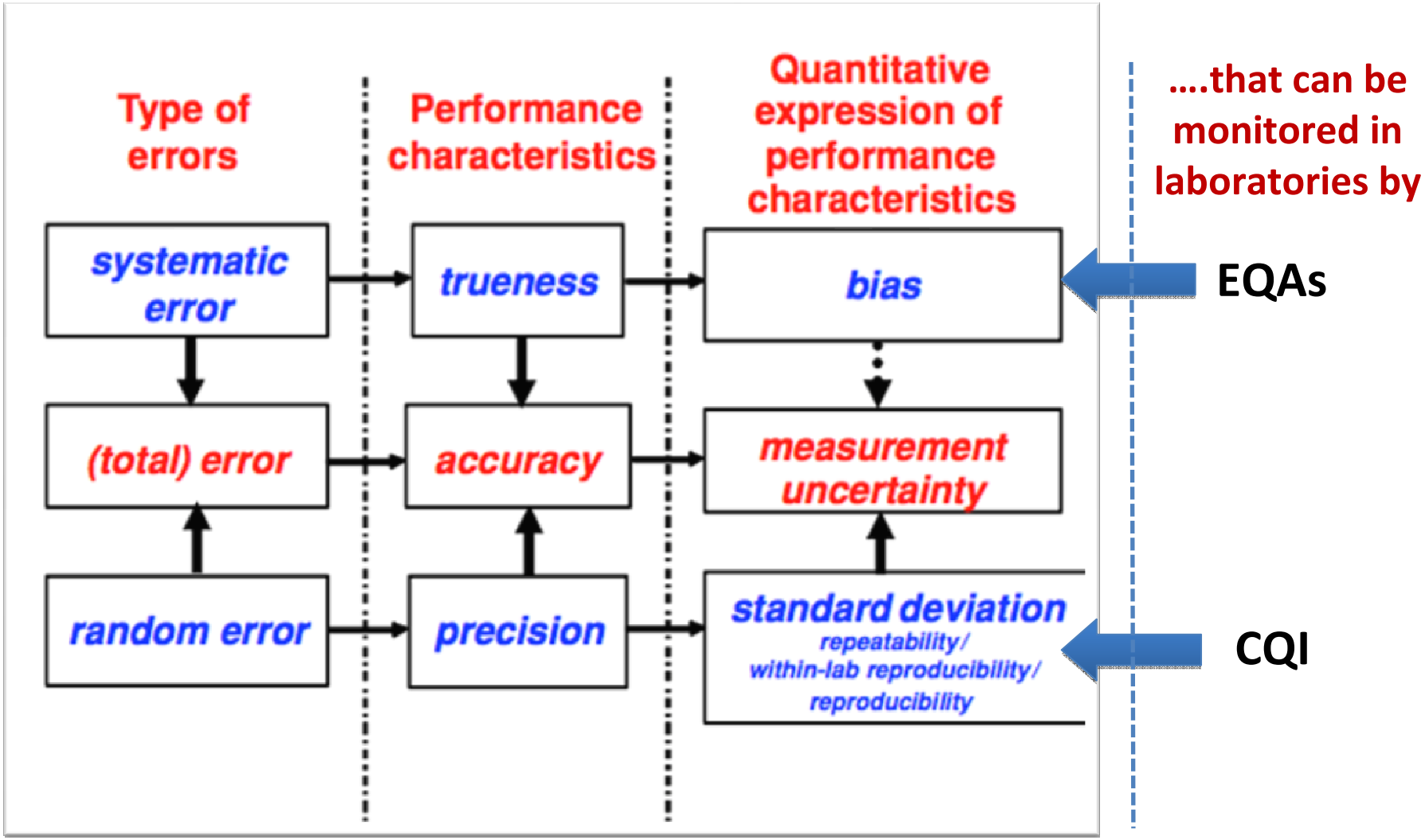
S-CA 19-9	***29,6***	kU/L	0,0 - 37,0	64,4	05/09/17

RCV

MU AND ERRORS IN MEASUREMENTS



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

COMBINED UNCERTAINTY AND PRE-ANALYTICAL ERRORS

$$u_c = \left(u_s^2 + u_B^2 + u_p^2\right)^{1/2}$$

$u_s = imprecision$

$u_B = bias$

$\boldsymbol{u_p = pre - analytical\ errors}$

"If ***pre-analytical errors*** may be neglected by assuring quality of samples/specimens, the equation may be reduced to .."

$$u_c = (u_s^2 + u_B^2)^{1/2}$$

Haeckel et al. CCLM 2015; 53:1161.

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 Patients safety

"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".

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 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
Test results is 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

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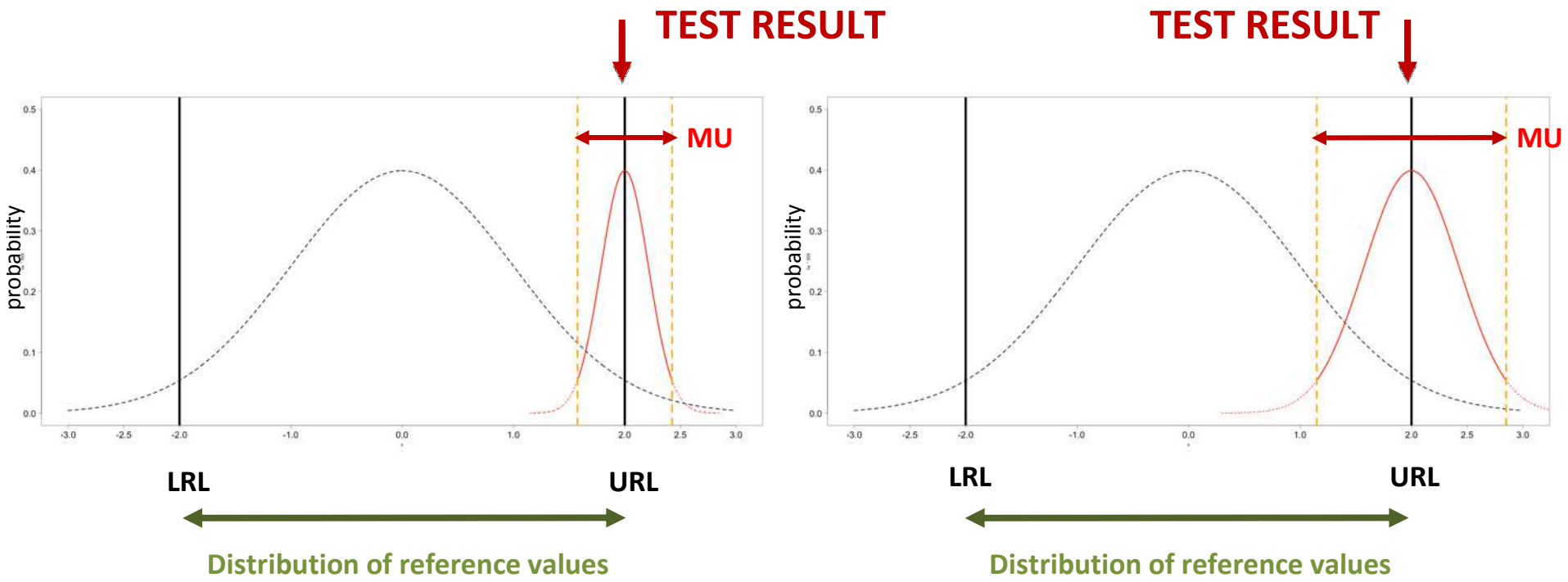
Test result is usually **compared with a cli decision point**		**Imprecision, bias and bias**
Test results is primarily used for **monitoring** patients over time		

Three different scenarios can exist

MU AND REFERENCE INTERVALS

THE THREE POSSIBLE SCENARIOS

Scenario 1: Test results are approximately overlapped to the the Upper (or the Lower) Reference Interval Limit (URL or LRL)

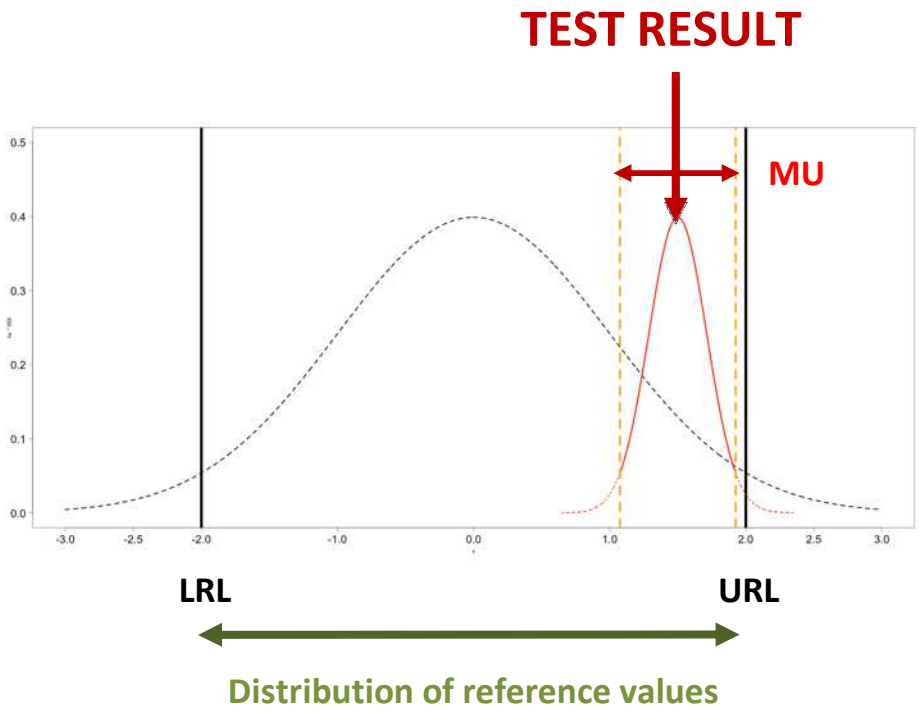


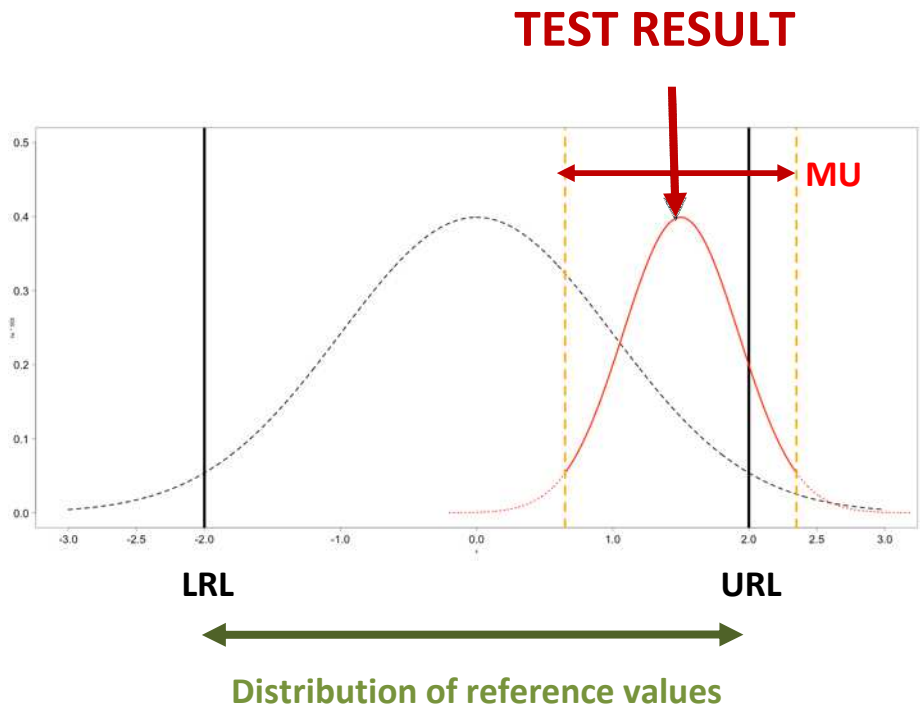
The inclusion of MU into laboratory reports does not change the clinical decision making process

MU AND REFERENCE INTERVALS

THE THREE POSSIBLE SCENARIOS

Scenario 2: Test results are within the Reference Interval Limit (1.5 times the standard deviation of the distribution reference values)



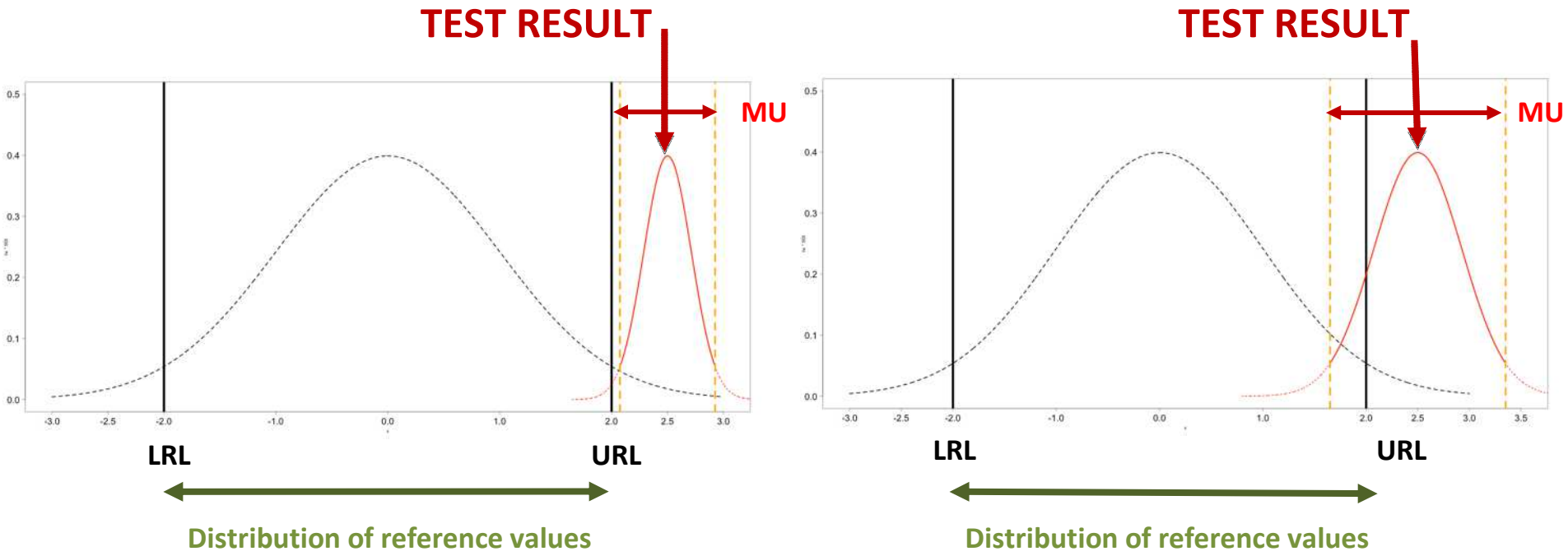


The inclusion of MU into laboratory reports changes the clinical decision making process when the test results plus MU encompass the URL (or LRL)

MU AND REFERENCE INTERVALS

THE THREE POSSIBLE SCENARIOS

Scenario 3: Test results are outside the Upper Reference interval limit (2.5 times the standard deviation of the distribution reference values)



The inclusion of MU into laboratory reports changes the clinical decision making process when the test results minus MU encompass the URL (or LRL)

REFERENCE INTERVALS AND MU

CLINICAL BIOCHEMISTRY (1)

Measurands (units)	Biological variation (from Westgard)			Individuality Index (II)*	Reference Intervals	
	CV_I (%)	CV_G (%)	CV_A (%)		LRL	URL
ALT (U/L)	19.4	41.6	4.4	0.48	10	50
Lactate (mmol/L)	27.2	16.7	2.4	1.64	0.5	2.2
Sodium (mmol/L)	0.6	0.7	0.9	1.55	136	145
Potassium (mmol/L)	4.6	5.6	0.7	0.83	3.4	4.5
Urea (mmol/L)	12.1	18.7	2.3	0.66	2.5	7.5
Cholesterol (mmol/L)	5.95	15.3	1.3	0.4	2	6.2

* Calculated by the Harris' formula. CV_A : laboratory-specific imprecision, estimated by IQC materials.

REFERENCE INTERVALS AND MU
CLINICAL BIOCHEMISTRY (2)

Measurands (units)	Reference Intervals		SD*	Target value (TV)* at 2.5 SD	MU derived interval for TV		Target value (TV)* at 1.5 SD	MU derived interval for TV	
	LRL	URL			Lower limit	Upper limit		Lower limit	Upper limit
ALT (U/L)	10	50	10.2	55.5	52.1	58.9	45.3	41.9	48.7
Lactate (mmol/L)	0.5	2.2	0.4	2.4	2.4	2.5	2	1.9	2.1
Sodium (mmol/L)	136	145	2.3	**146.2**	**144**	**148.5**	**143.9**	**141.7**	**146.2**
Potassium (mmol/L)	3.4	4.5	0.3	4.7	4.6	4.7	4.4	4.3	4.4
Urea (mmol/L)	2.5	7.5	1.3	8.2	7.9	8.4	6.9	6.7	7.2
Cholesterol (mmol/L)	2	6.2	1.1	6.8	6.6	6.9	5.7	5.6	5.8

* SD and TV is calculated by using the RI as suggested by Haeckel et al. CCLM 2015; 53:1161.

MU NOTIFIED IN MEDICAL REPORTS: PROBABILITY OF RE-TESTING

CLINICAL BIOCHEMISTRY

Measurands (units)	Reference Intervals		SD_A	SD	SD_A/SD	Probability of Retesting*
	LRL	URL				
ALT (U/L)	10	50	1.7	10.2	0.17	2.51
Lactate (mmol/L)	0.5	2.2	0.04	0.4	0.09	1.32
Sodium (mmol/L)	136	145	1.13	2.3	0.49	**8.61**
Potassium (mmol/L)	3.4	4.5	0.03	0.3	0.11	1.32
Urea (mmol/L)	2.5	7.5	0.12	1.3	0.09	1.20
Cholesterol (mmol/L)	2	6.2	0.06	1.1	0.06	0.65

SD_A : laboratory-specific imprecision, estimated by IQC materials.

* Derived from Monte Carlo Simulation results, $p>0.05$ was considered significant.

REFERENCE INTERVALS AND MU
COAGULATION AND HEMATOLOGY (1)

Measurands (units)	Biological variation (from Westgard)		CV_A (%)	Individuality Index (II) *	Reference Intervals	
	CV_I (%)	CV_G (%)			LRI	URI
Haemoglobin (g/L)	2.85	6.8	0.82	0.44	140	175
MCV (fL)	1.4	4.85	0.7	0.32	80	96
S-Protein (%)	5.8	63.4	2.6	0.1	74	146
C-Protein (%)	5.6	55.2	2.9	0.11	70	140
D-Dimer (µg/L)	23.3	26.5	6.25	0.91	0	400

* Calculated by the Harris' formula.

CV_A : laboratory-specific imprecision estimated by IQC materials.

REFERENCE INTERVALS AND MU

COAGULATION AND HEMATOLOGY (2)

Measurands (units)	Reference Intervals		SD*	Target value (TV)* at 2.5 SD	MU derived interval for TV		Target value (TV)* at 1.5 SD	MU derived interval for TV	
	LRL	URL			Lower limit	Upper limit		Lower limit	Upper limit
Haemoglobin (g/L)	140	175	8.9	179.8	179.5	180.1	170.9	170.6	171.2
MCV (fL)	80	96	4.1	98.2	97.1	99.3	94.1	93	95.2
S-Protein (%)	74	146	18.4	**155.9**	**144.9**	**166.9**	**137.6**	**126.6**	**148.6**
C-Protein (%)	70	140	17.9	149.6	148.1	151.2	131.8	130.2	133.2
D-Dimer (µg/L)	0	400	102	455.1	421.5	488.7	353.1	319.5	386.7

* SD and TV are calculated by RI as suggested by Haeckel et al. CCLM 2015; 53:1161.

MU NOTIFIED IN MEDICAL REPORTS: PROBABILITY OF RE-TESTING

COAGULATION AND HEMATOLOGY

Measurands (units)	Reference Intervals		SD_A	SD_T	SD_A/SD_T	Probability of Retesting*
	LRL	URL				
Haemoglobin (g/L)	140	175	0.14	8.9	0.02	0.18
MCV (fL)	80	96	0.55	4.1	0.13	1.89
S-Protein (%)	74	146	5.5	18.4	0.30	5.76
C-Protein (%)	70	140	0.77	17.9	0.04	0.51
D-Dimer (μg/L)	0	400	6.25	102	0.16	2.47

SD_A : laboratory specific imprecision estimated by IQC materials.

* Derived from Monte Carlo Simulation results, $p>0.05$ was considered significant.

REFERENCE INTERVALS AND MU
FLOW CYTOMETRY AND HEMATOLOGY (1)

Measurands (units)	Reference Intervals		SD_A	SD_T	SD_A/SD_T
	LRL	URL			
CD3+ (%)	58	80	0.46	5.61	0.08
CD8+ (%)	16	33	0.53	4.33	0.12
CD4+ (%)	32	51	0.65	4.84	0.13
CD19+ (%)	7	21	0.37	3.57	0.10
CD16+/CD56+ (%)	7	26	0.38	4.8	0.08

REFERENCE INTERVALS AND MU

FLOW CYTOMETRY AND HEMATOLOGY (2)

Measurands (units)	Reference Intervals		SD*	Target value (TV)* at 2.5 SD	MU derived interval for TV		Target value (TV)* at 1.5 SD	MU derived interval for TV	
	LRL	URL			Lower limit	Upper limit		Lower limit	Upper limit
CD3+ (%)	58	80	0.46	83.0	82.1	84.0	77.4	76.5	78.3
CD8+ (%)	16	33	0.53	35.3	34.3	36.4	31.0	29.9	32.1
CD4+ (%)	32	51	0.65	53.6	52.3	54.9	48.8	47.5	50.1
CD19+ (%)	7	21	0.37	22.9	22.2	23.7	19.4	18.6	20.1
CD16+/CD56+ (%)	7	26	0.38	28.6	27.9	29.4	23.8	23.0	24.5

No significant differences were found by including MU to test results at TVs of 1.5 SD and 2.5 SD !!

MU AND FIT-FOR-PURPOSE OF TEST RESULTS

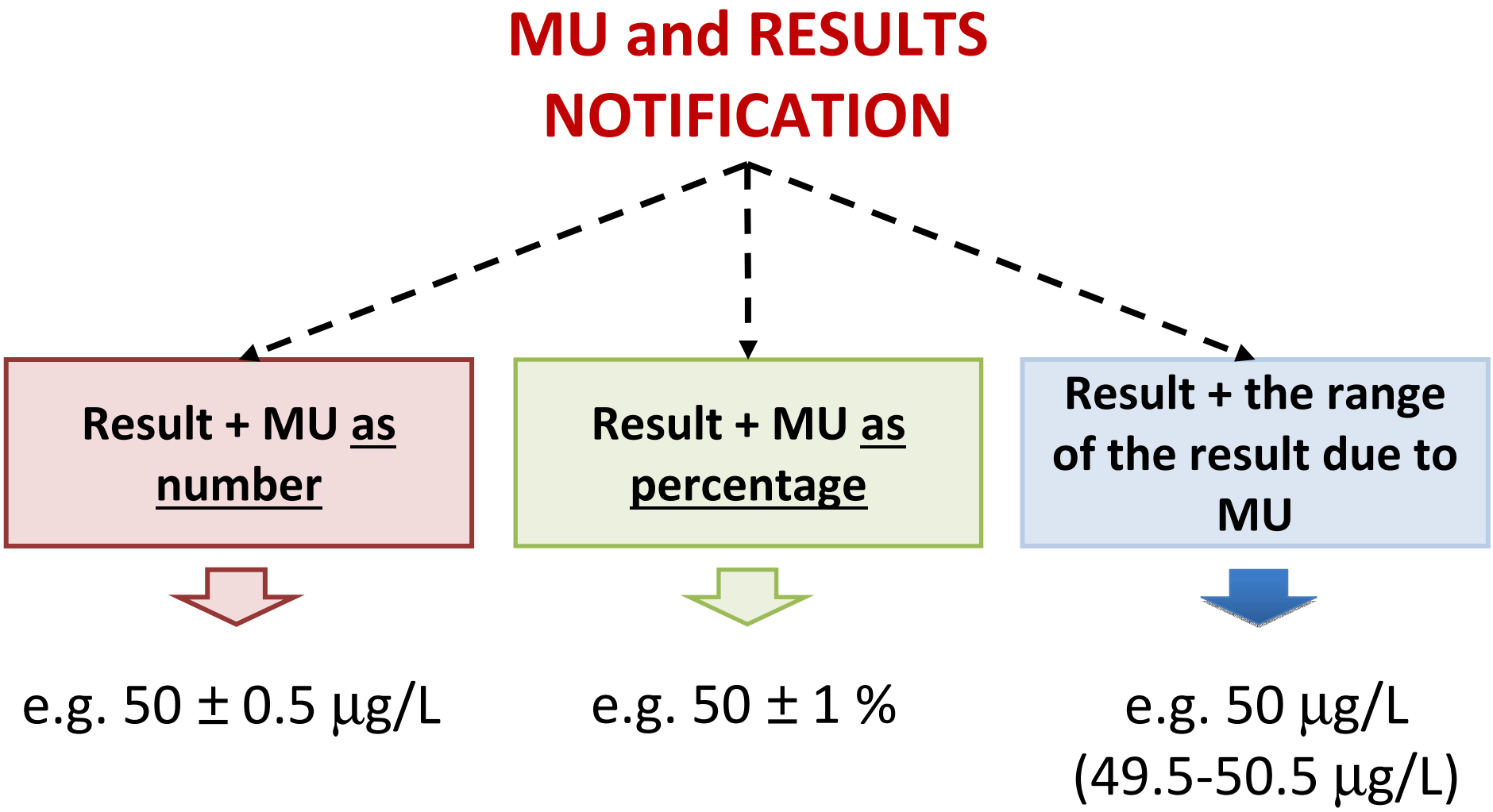
Test Purposes and Uncertainty: components to be included

Test purpose	Examples	Components to be included in measurement uncertainty
Test 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
Test results is 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

DECISION LIMITS AND MEASUREMENT UNCERTAINTY

Measurands (units)	MU	Decision limit	Significant value based on MU
Glucose (mmol/L)	**0.4**	7.0	7.4
HbA1c (mmol/mol)	**3.6**	48.0	51.6
tPSA (mg/L)	**1.0**	4.0	5.0
Troponin (ng/L)	**2.7**	16.0	18.7

RESULTS NOTIFICATION



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REFERENCE CHANGE VALUE (RCV) AND MU

Measurands (units)	MU	Hypothetical result at the decision limit	Significant variation based on RCV*	Significant variation based on MU#
CEA (µg/L)	**1.4**	5	**6.8**	**6.9**
CA 15-3 (kU/L)	**3.2**	37.5	45.0	42.0
CA 125 (kU/L)	**9.2**	48	84.9	61.0
CA 19-9 (kU/L)	**5.2**	37	55.7	44.3
AST (U/L)	**11.0**	45	60.7	60.4
Creatinine (µmol/L)	**4.0**	104	121.3	109.7

* Calculated by the Harris' formula for RCV
# Calculated by the CLSI EP29 formula

CLINICAL MOLECULAR BIOLOGY
THE BCR-ABL1 EXAMPLE

ELN European LeukemiaNet

UPDATE 2013

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Response definitions for any TKI first line, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL^{IS} ≤0.1%* (MMR)	BCR-ABL^{IS} 0.1-1%*	BCR-ABL^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

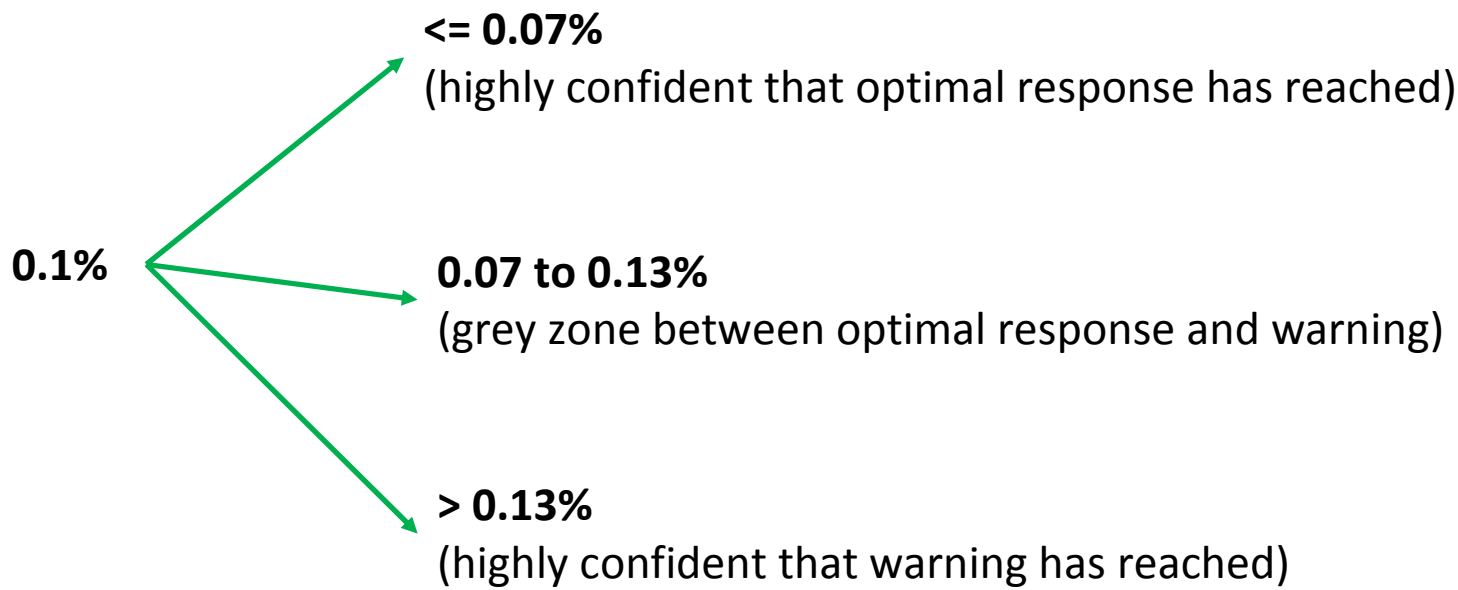
CLINICAL MOLECULAR BIOLOGY
THE BCR-ABL1 MU

Measurands (units)	MU	Hypothetical test result at 12 months	Significant variation based on MU#
BCR/ABL %	**0.03**	0.1%	0.07-0.13%

CLINICAL MOLECULAR BIOLOGY
BCR-ABL1 RESULTS INTERPRETATION

ELN LeukemiaNet 2013

Significant value based on MU



CLINICAL MOLECULAR BIOLOGY
THE JAK2 V617F EXAMPLE

bjh guideline

Molecular diagnosis of the myeloproliferative neoplasms: UK guidelines for the detection of *JAK2* V617F and other relevant mutations

Anthony J. Bench,[1] Helen E. White,[2,3] Letizia Foroni,[4] Anna L. Godfrey,[5] Gareth Gerrard,[4] Susanna Akiki,[6] Abida Awan,[7] Ian Carter,[8] Andrea Goday-Fernandez,[1] Stephen E. Langabeer,[9] Tim Clench,[10] Jordan Clark,[11] Paul A. Evans,[12] David Grimwade,[13] Anna Schuh,[14] Mary F. McMullin,[15] Anthony R. Green,[5] Claire N. Harrison[16] and Nicholas C. P. Cross[2,3]

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CLINICAL MOLECULAR BIOLOGY
THE JAK2 V617F MU

Measurands (units)	MU	Hypothetical test result	Significant value for MU (based on decision limit)
JAK 2 V617F* **(cut-off 1%)**	**0.54**	1%	0.46-1.54%
	5.9	10%	4.1-15.9%

*Bias estimated vs first WHO Reference Panel for Genomic Jak2 V617F, NIBSC code: 16/120

CLINICAL MOLECULAR BIOLOGY
Jak2 V617F RESULTS INTERPRETATION

JAK2 V617F guideline

1 % (allelic burden)

Clinical relevant threshold

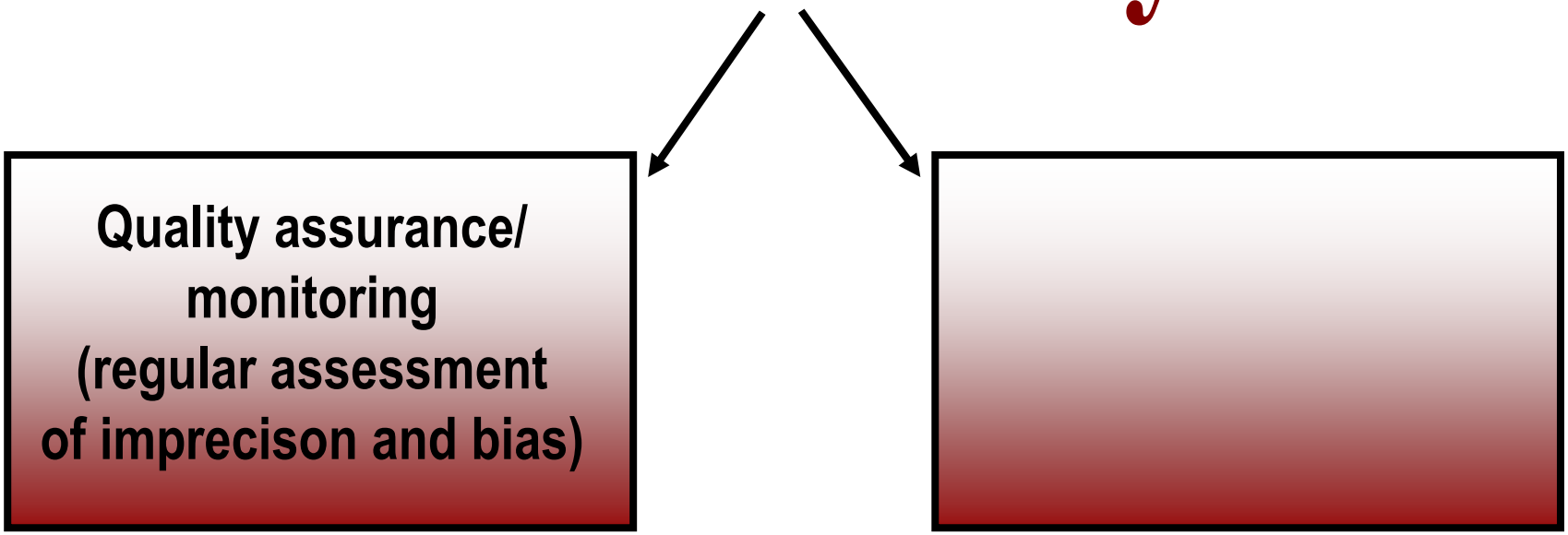
Significant value based on MU

<= 0.46% (highly confident that the result is below the clinically relevant threshold)

0.46 to 1.54% (grey zone)

> 1.54 % (highly confident that the result is positive and above the clinically relevant threshold)

Measurement Uncertainty



A PIECE OF THE PUZZLE

Other fundamental information in a laboratory report:

a)Right measurement ***units***

b)Right reference intervals

c)Right ***decision limits*** (threshold)

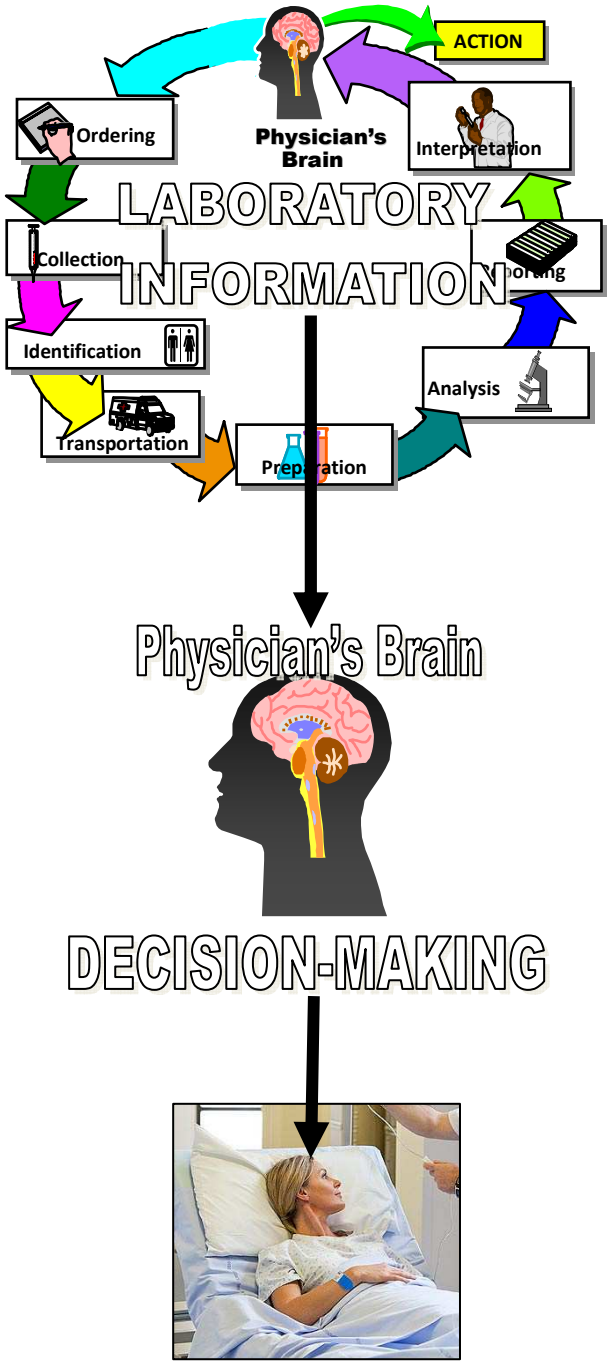
d)Right ***interpretative comments***

e)Right ***critical results notification***

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


ACTION
Ordering
Physician's Brain
Interpretation
LABORATORY
INFORMATION
Collection
Identification
Analysis
Transportation
Preparation
Physician's Brain
DECISION-MAKING

Criteria for Quality Testing

- **Right** test, for the right patient
- **Right** time for specimen collection
- **Right** specimen and processing

Pre-analytical

- **Right** test result generated

Analytical

- **Right** test result reported, acknowledged and interpreted

Post-analytical

"Wrongs" anywhere compromise test result ***quality*** *and* ***patients' safety****!*

Thank you for your attention!

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