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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

site: http://users.unimi.it/cirme

12th International Scientific Meeting

STANDARDIZATION IN LABORATORY MEDICINE AND PATIENT SAFETY

EVERY DAY IS PATIENT SAFETY DAY

MILANO, ITALY
November 29th, 2018

Standardization: a bumpy but necessary path

Mauro Panteghini

University of Milan Medical School

Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Drivers for global standardization in laboratory medicine

- Clinical governance and guidelines (EBM)
- Laboratory accreditation, consolidation and networking
- Advances in IT and electronic health records

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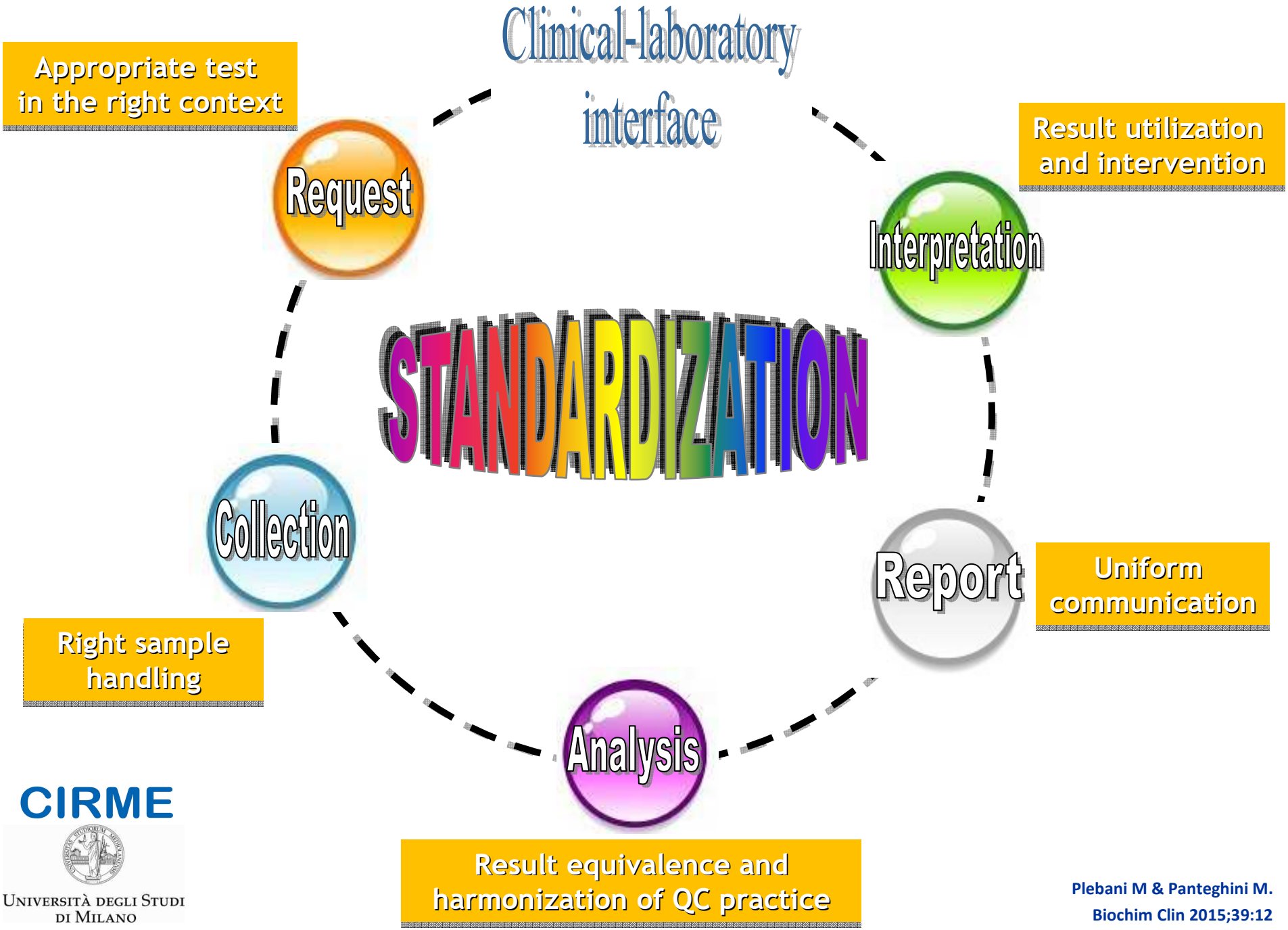

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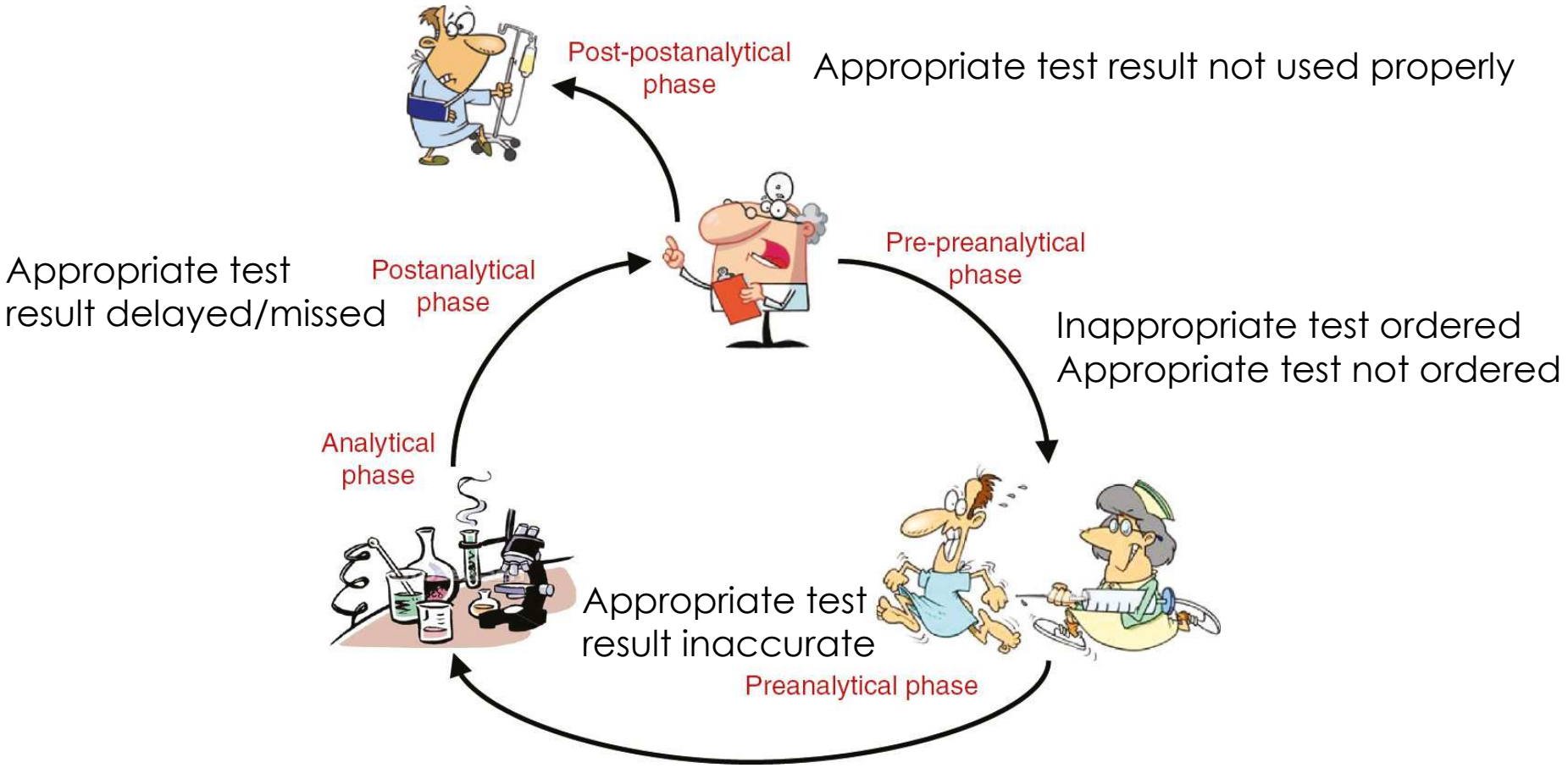
Plebani M & Panteghini M.
Biochim Clin 2015;39:12

Lab-related causes of diagnostic mistakes



"Wrongs" anywhere compromise ***test result quality*** *and* ***patient safety****!*

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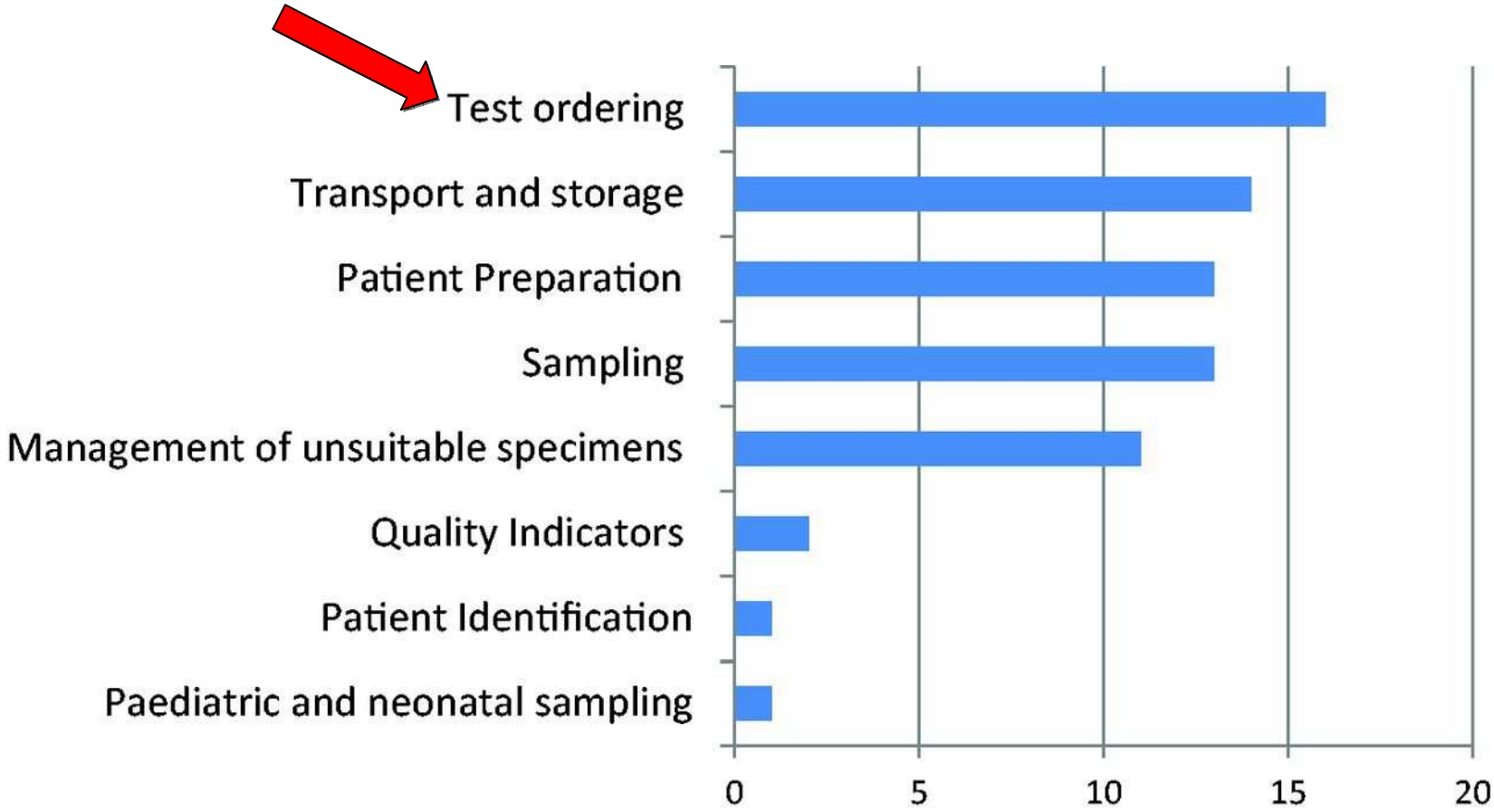
Patient Safety

Vignette from Lippi G & Simundic AM. CCLM 2018;56:1660

Key preanalytical steps identified as the most critical and in need of immediate standardization



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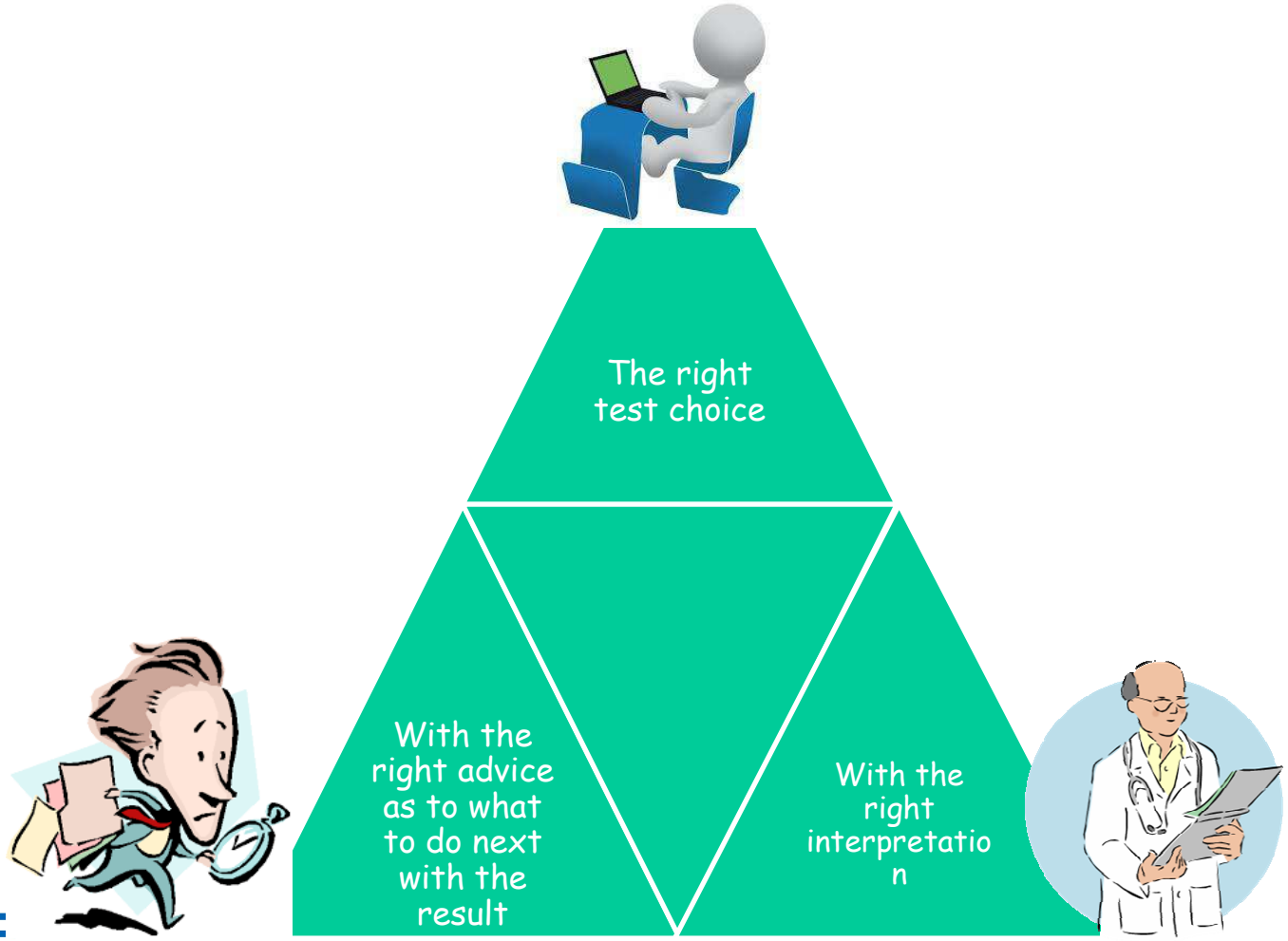
Michael P Cornes et al. Ann Clin Biochem 2016;53:539-547

EFLM

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

The triad of elements of value in laboratory information



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Ferraro S & Panteghini M. Clinical Biochemistry 50 (2017) 555–561

NHS England Atlas of Diagnostic Variation

- 72-fold difference in PSA requesting between most and least requesting groups of GPs
- 89-fold difference in BNP requesting
- 106-fold difference in annual rate of creatinine requesting
- 446-fold difference in calprotectin
- 4/5-fold difference in average even when outliers are removed

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Why we need to reduce variation in test requests?

"…the existence of persistent unwarranted variations in health care directly impacts on equity of access to services, the health outcomes of populations and efficient use of resources."

Appleby J, Raleigh V (2011) Variations in Health Care – the Good, the Bad & the Inexplicable. The King's Fund. http://www.kingsfund.org.uk/audio-video/john-appleby-variations-health-care

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Clinical Biochemistry 54 (2018) 85–91

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Are laboratory tests always needed? Frequency and causes of laboratory overuse in a hospital setting☆

Janne Cadamuro[a,*], Martin Gaksch[a], Helmut Wiedemann[a], Giuseppe Lippi[b], Alexander von Meyer[c], Astrid Pertersmann[d], Simon Auer[a], Cornelia Mrazek[a], Ulrike Kipman[e], Thomas K. Felder[a], Hannes Oberkofler[a], Elisabeth Haschke-Becher[a]

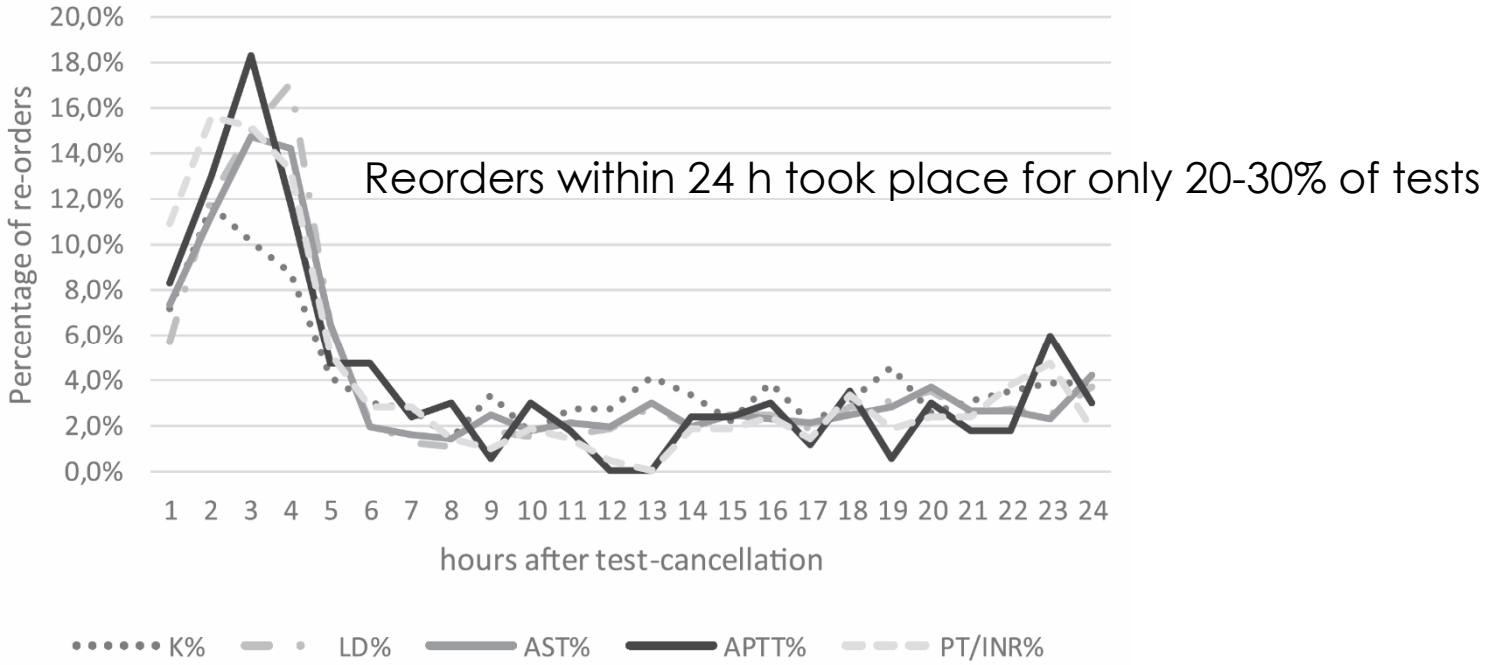

Fig. 2. Time course of re-orders after initial test cancellation.

Types of interventions to improve appropriateness and standardize test request

- ✓ Developing and disseminating practice care maps (agreed in partnership with clinicians), using HTA approach when guidelines are lacking
- ✓ Deleting obsolete tests from laboratory order forms
- ✓ Avoiding pathophysiologic duplications
- ✓ Gating policies - Traffic Light Systems (particularly for complex and costly tests)
- ✓ Restricting retesting (minimum retesting intervals)

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Ferraro S & Panteghini M. Clinical Biochemistry 50 (2017) 555–561

Opinion Paper

Giuseppe Lippi[a,*], Mauro Panteghini[a], Sergio Bernardini[a], Laura Bonfanti[b], Paolo Carraro[a], Ivo Casagranda[b], Mario Cavazza[b], Ferruccio Ceriotti[a], Marcello Ciaccio[a], Daniele Coen[b], Davide Giavarina[a], Fabrizio Giostra[b], Ciro Paolillo[b], Mario Plebani[a], Giorgio Ricci[b] and Gianfranco Cervellin[b]

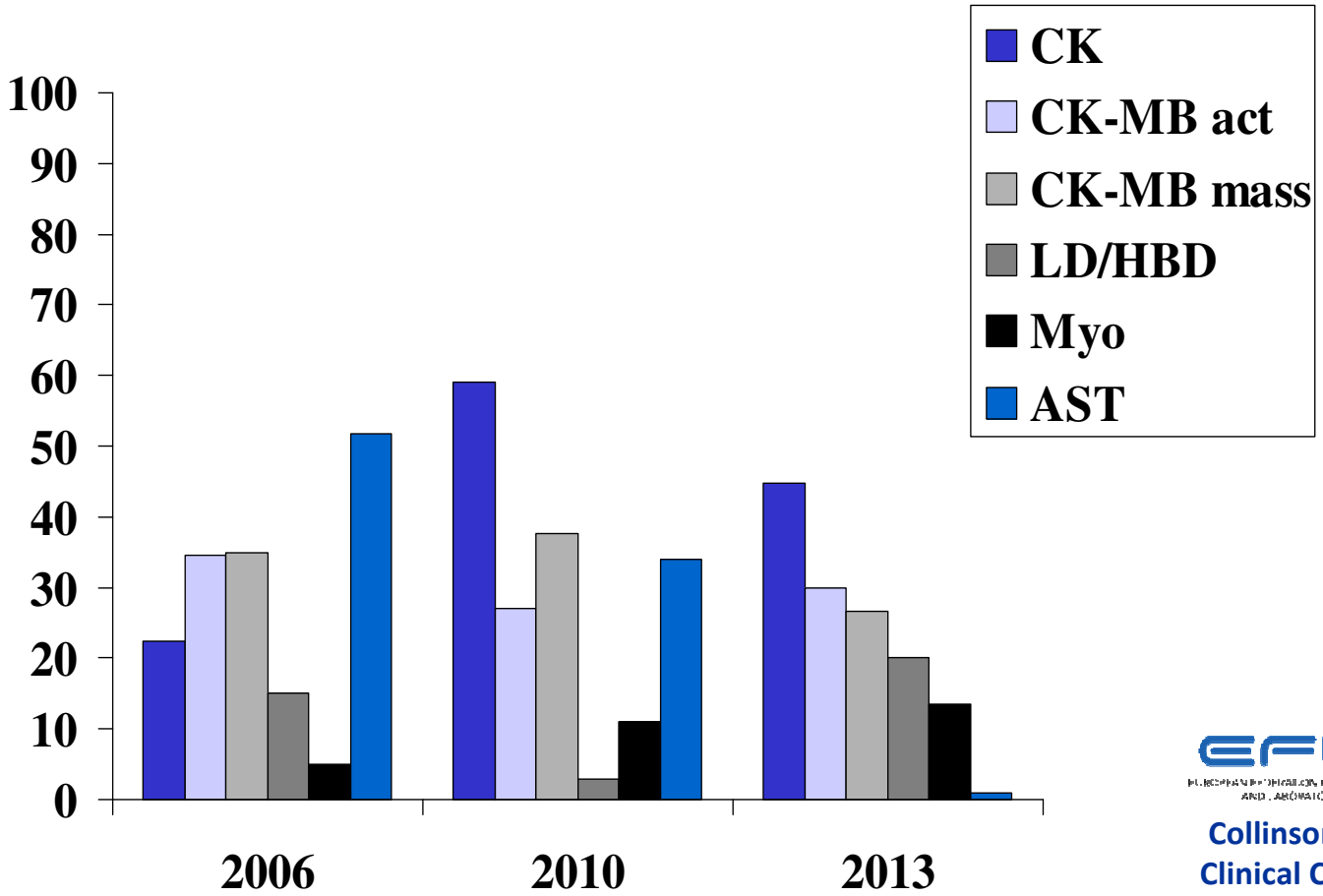
Laboratory testing in the emergency department: an Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) and Academy of Emergency Medicine and Care (AcEMC) consensus report

the parameters were finally classified as "strongly recommended" (mean value, 1.00–1.49), "weakly recommended" (mean value, 1.50–1.99), "discouraged" (mean value, 2.00–2.49) and "strongly discouraged" (mean value, 2.50–3.00).

Parameters	Overall	SIBioC	AcEMC	p-Value[a]	Recommendation
Acute pancreatitis					
Amylase (total)	2.50 (0.87)	2.75 (0.66)	2.25 (0.97)	0.14	Discouraged
Amylase (pancreatic)	2.00 (0.71)	1.88 (0.78)	2.13 (0.60)	0.26	Discouraged
Lipase	1.25 (0.43)	1.25 (0.43)	1.25 (0.43)	0.50	**Strongly recommended**
Infection					
White blood cell count (WBC)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00	**Strongly recommended**
C-reactive protein	1.13 (0.33)	1.00 (0.00)	1.25 (0.43)	0.07	**Strongly recommended**
Procalcitonin	1.81 (0.53)	1.63 (0.70)	2.00 (0.00)	0.09	Weakly recommended
Presepsin	2.88 (0.33)	2.88 (0.33)	2.88 (0.33)	0.50	Strongly discouraged
Lactate	1.19 (0.39)	1.13 (0.33)	1.25 (0.43)	0.28	**Strongly recommended**
Acute myocardial infarction					
Cardiac troponin I or T (cTnI or cTnT)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00	**Strongly recommended**
Creatine kinase MB (CK-MB)	2.69 (0.58)	3.00 (0.00)	2.38 (0.70)	0.02	Strongly discouraged
Myoglobin	2.94 (0.24)	2.88 (0.33)	3.00 (0.00)	0.17	Strongly discouraged
Natriuretic peptides	2.25 (0.56)	1.88 (0.33)	2.63 (0.48)	<0.01	Discouraged

Markers still used for the diagnosis of AMI in addition to cardiac troponin

The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) Study of the EFLM WG Cardiac Markers



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EFLM

Collinson P et al., Clinical Chemistry 62:9 1264–1271 (2016)

✓ Avoid pathophysiologic duplications

The "famous pairs" in laboratory medicine.

- Serum creatinine and urea
- Erythrocyte sedimentation rate and C-reactive protein
- Aspartate aminotransferase and alanine aminotransferase
- Total and conjugated bilirubin
- Amylase and lipase
- Prothrombin time and activated partial thromboplastin time
- Free T_3 and free T_4
- Total and free prostate specific antigen
- Ferritin and transferrin saturation

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Ferraro S & Panteghini M. Clinical Biochemistry 50 (2017) 555–561

Limiting the testing of AST

Testing of AST in addition to ALT should be limited because:

- ALT is the more liver-specific enzyme. Moreover, increases of ALT activity persist longer than AST.
- The incremental benefit of routine determination of AST, in addition to ALT, is limited.
- Laboratories reporting abnormal ALT results (ie, >twice the URL) should offer AST as a reflex test and calculate the AST-to-ALT ratio because it provides useful diagnostic and prognostic information.

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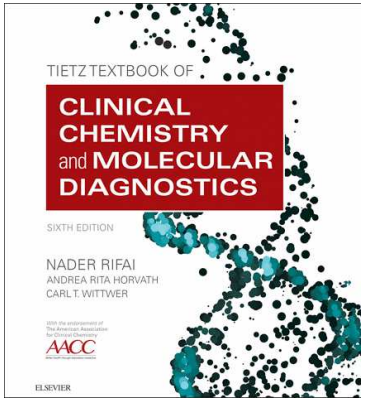
Panteghini M, Bais R. Serum enzymes. In: "Tietz Textbook of Clinical Chemistry and Molecular Diagnostics". 6th ed. Elsevier Saunders: St. Louis, 2018



Sistema Socio Sanitario

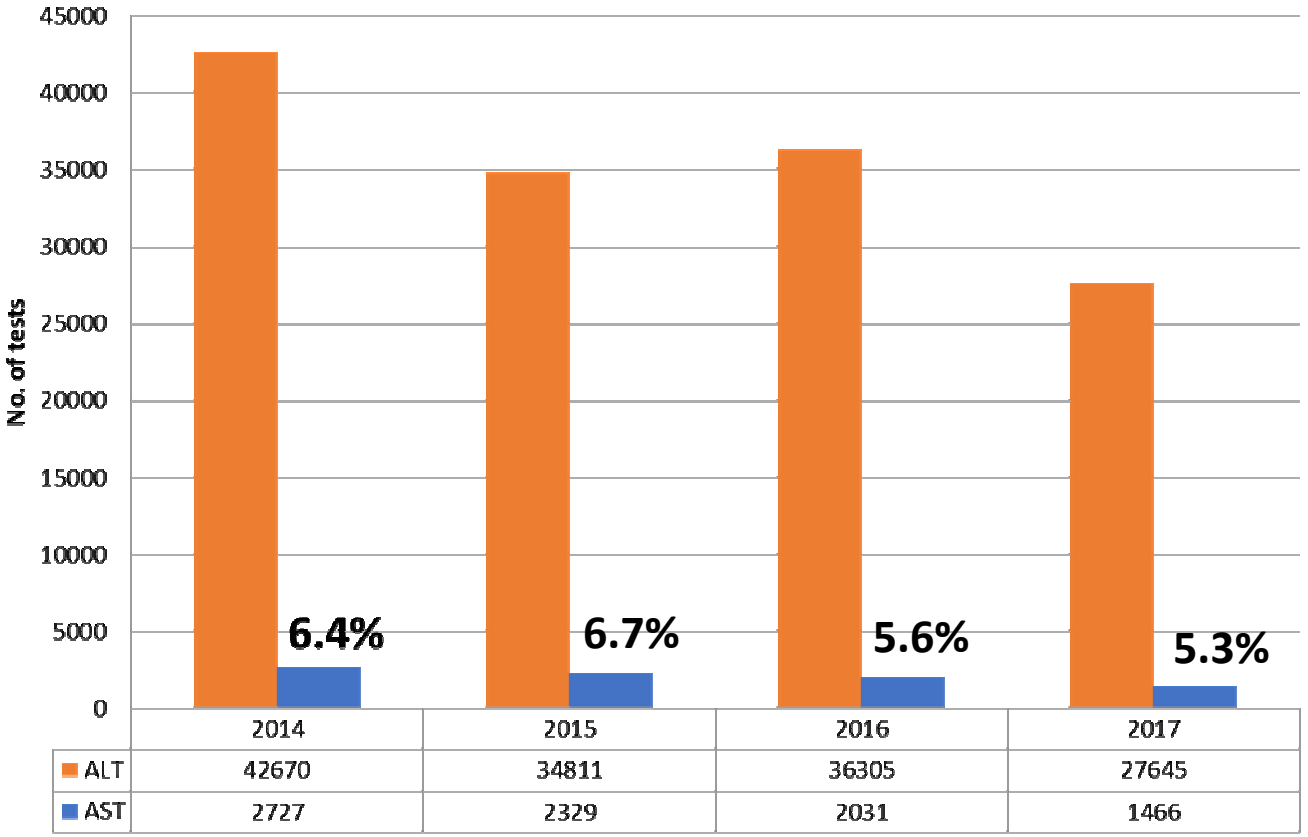
Regione Lombardia

ASST Fatebenefratelli Sacco

Offering Aspartate Aminotransferase as a Reflex Test: An Easy but Effective Way to Improve Appropriateness of Laboratory Requests

Am J Clin Pathol May 2018;149:456-457

Sarah Birindelli, MSc
Sara Pasqualetti, MSc
Mauro Panteghini, MD
Clinical Pathology Unit
ASST Fatebenefratelli-Sacco
Milan, Italy



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Characteristics of Tests Performed in 2010 on Calgary Area Residents That Were Inappropriately Repeated[a]

Test Type	Annual Test Count at the Study Laboratory	Percentage Repeated Inappropriately (95% Confidence Interval)	Recoverable Internal Cost of Each Test for the Study Laboratory (CAD)[b]	Annualized Cost of Inappropriate Repeats at the Study Laboratory (Millions)
Cholesterol	470,645	10.5 (10.3-10.7)	$1.00-$5.00	$0.05-$0.25
HbA_{1c} with normal result[c]	111,225	31.3 (30.7-31.9)	$2.00-$7.00	$0.07-$0.24
HbA_{1c} with abnormal result[d]	121,470	24.8 (24.3-25.3)	$2.00-$7.00	$0.06-$0.21
TSH	532,475	7.2 (7.0-7.3)	$1.00-$5.00	$0.04-$0.19
Vitamin B_{12}	143,150	28.4 (27.8-28.9)	$2.00-$7.00	$0.08-$0.29
Vitamin D with normal result[c]	57,930	24.5 (23.8-25.3)	$5.00-$13.00	$0.07-$0.18
Ferritin with normal result[c]	275,700	35.8 (35.4-36.2)	$2.00-$8.00	$0.2-$0.79
All tests[e]	1,867,315	16.4 (16.3-16.6)	NA	$0.57-$2.15

Adapted from Morgen EK et al. Am J Clin Pathol 2015;144:704.

Annual savings achievable eliminating the inappropriate testing in the study institution. Corresponds to a national annual cost of 160 million $ CAD (~110 million €)

Test Name, Minimum ITT (Days)	2017		2016			2015		
	Lanzoni et al[36,b]	Chami et al[37]	Current Study[b]	Demir et al[39,b]	Pelloso et al[38,b]	Lippi et al[15,b]	Smit et al[40,b,c]	Morgen and Naugler[41,d]
Lipid panel, 28	24	10	5	4[f]		44[f]	6	5[f]
TSH, 28		8	6			17[f]		3[f]
Hemoglobin A_{1c}, 90		18	4			24[f]	4	15[f]
CRP, 1			13			4[f]	11	
Iron, 60			8					
Ferritin, 90	0		10			28[f]		12[f]
Folate, no repeats	16	20	5		10[f]	35[f]		
25-Hydroxyvitamin D, 90	10	7	7		15[f]			5[f]
1,25-Dihydroxyvitamin D, 90	6		3					
CDIFFPCR, 7			3					
PCT, 1			14			5[f]		
Total average	11	13	7	4	13	22	7	8

CDIFFPCR, *Clostridium difficile* by polymerase chain reaction; CRP, C-reactive protein; ITT, intertest time; PCT, procalcitonin; TSH,
[a]Values shown are as percentages. All percentages are determined based on the total volume of testing for each specific test. All studies i

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Specialists were more likely than primary care physicians to order repeat tests too soon.

Prevention is better than cure: stopping inappropriate requests before they reach the laboratory

Fryer AA & Smellie WSA. J Clin Pathol 2013;66:62.
Ferraro S & Panteghini M. Clin Biochem 2017;50:555.

Computerised physician order entry systems

Institutions should fully exploit the potential of electronic requesting acting as "enabling factor" for reinforcing educational messages and sustaining their effects over time.

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Effectiveness of Practices to Support Appropriate Laboratory Test Utilization

A Laboratory Medicine Best Practices Systematic Review and Meta-Analysis

Matthew Rubinstein, MS,[1] *Robert Hirsch, PhD,*[2] *Kakali Bandyopadhyay, PhD,*[3]

Am J Clin Pathol **March 2018;149:197**

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Summary of Practice Recommendations

Practice Category	Practice Recommendation
CPOE	Use of CPOE is recommended as a best practice to support appropriate clinical LTU
CDSS/CDST	No recommendation for or against due to insufficient evidence is made for CDSS/CDST as a best practice to support appropriate clinical LTU
Education	No recommendation for or against due to insufficient evidence is made for education as a best practice to support appropriate clinical LTU
Feedback	No recommendation for or against due to insufficient evidence is made for feedback as a best practice to support appropriate clinical LTU
Reflex testing	Use of reflex testing practices is recommended as a best practice to support appropriate clinical LTU
Test review	No recommendation for or against due to insufficient evidence is made for test review as a best practice to support appropriate clinical LTU
LTU team	No recommendation for or against due to insufficient evidence is made for LTU team as a best practice to support appropriate clinical LTU
Combined practices	Use of combined practices is a recommended as a best practice to support appropriate clinical LTU

CDSS/CDST, clinical decision support systems/tools; CPOE, computerized provider order entry; LTU, laboratory test utilization.

The way forward: CPOE standardization

- For any institution trying to achieve optimum patient care (and control costs), the appropriate design of information systems for CPOE is critical.
- Consequently, laboratory professionals must insist that information system vendors provide effective systems to assist in the insitutions' endeavors to ensure appropriate test requests.

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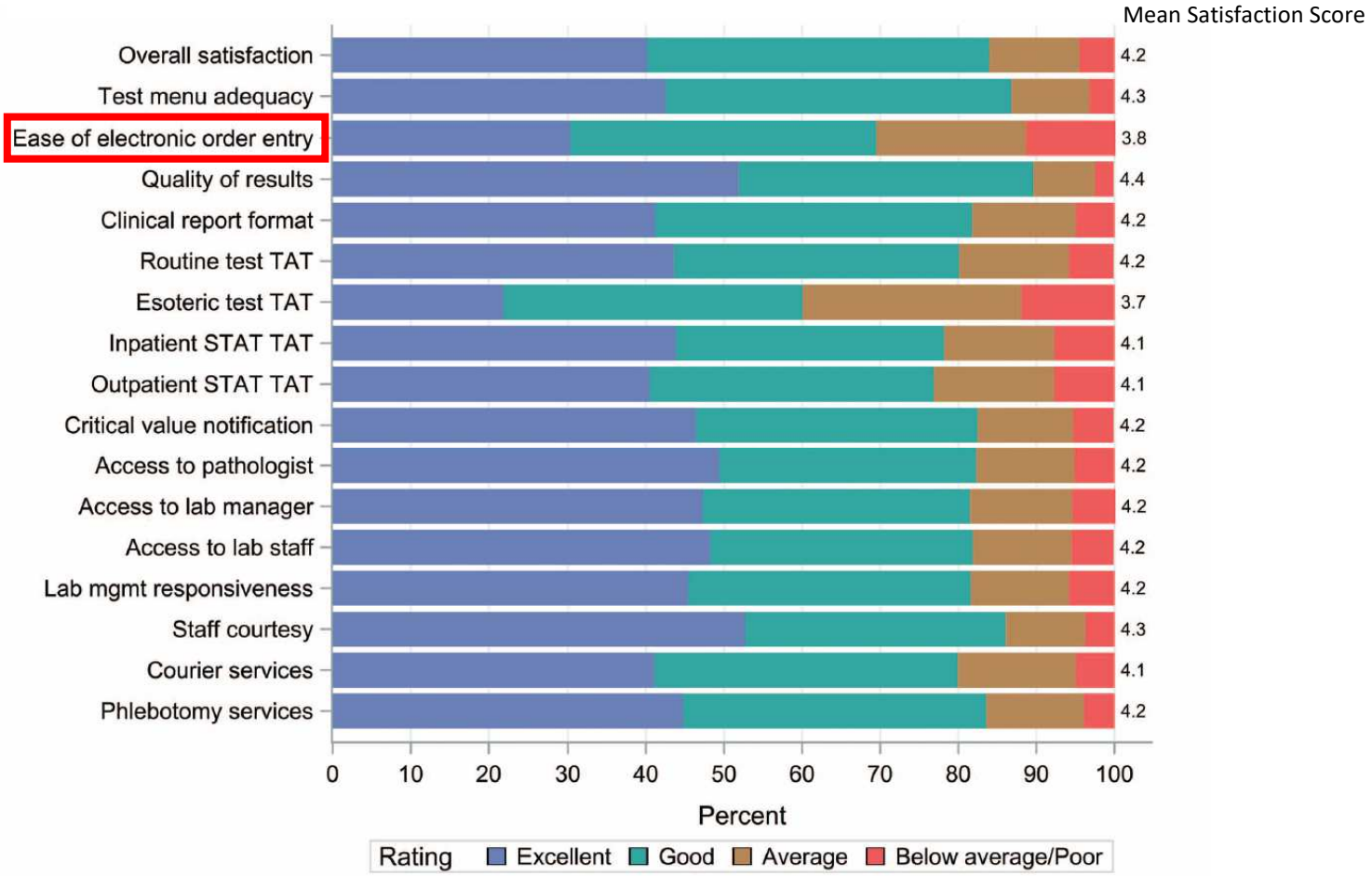
The Phoenix

Clinicians' satisfaction with laboratory services: CPOE performance as a new challenge

Computerised physician order entry systems



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McCall SJ et al. Arch Pathol Lab Med. 2016;140:1098

Underutilization in laboratory testing: an underappreciated problem

Characteristic	Error rate (95% CI)	Difference (95% CI)	n
Subgroup			
Overutilization	20.6 (16.2, 24.9)	(reference)	114
Underutilization	44.8 (33.8, 55.8)	24.2 (12.5, 36.0)	18
Overutilization			
Initial testing	43.9 (35.4, 52.5)	(reference)	18
Repeat testing	7.4 (2.5, 12.3)	−36.5 (−46.4, −26.7)	55
Both	28.0 (22.2, 33.8)	−15.9 (−5.6, −26.3)	41

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Zhi M et al. PLoS ONE 2013;8:e78962.

The Association for
Clinical Biochemistry &
Laboratory Medicine
Better Science, Better Testing, Better Care

Annals of Clinical Biochemistry
2018, Vol. 55(2) 281–286
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DOI: 10.1177/0004563217716475
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SAGE

Urinary albumin: a risk marker under-requested in primary care in Spain

Maria Salinas[1,2], Maite López-Garrigós[1], Emilio Flores[1,3] and Carlos Leiva-Salinas[4]; on behalf of the Pilot Group of the Appropriate Utilization of Laboratory Tests

Underutilization of albuminuria results in morbidity due to delayed diagnoses and missed early interventions

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(*Arch Pathol Lab Med.* 2006;130:1106–1113)

Identification Errors Involving Clinical Laboratories

A College of American Pathologists Q-Probes Study of Patient and Specimen Identification Errors at 120 Institutions

Paul N. Valenstein, MD; Stephen S. Raab, MD; Molly K. Walsh, PhD

PATIENT SAFETY

Table 4. Reasons for 4852 Identification Errors

Reason for Identification Error	No. of Errors	%
Primary specimen label error	2691	55.5
Initial registration/order entry error	1088	22.4
Other clerical error	604	12.4
Other reason for error	205	4.2
Aliquot/block/slide label error	184	3.8
Result entry error	80	1.7

Table 5. Frequency of Adverse Event Types (N = 345)

Type of Event	No. of Adverse Events	%
Significant patient inconvenience; no known change in treatment or patient outcome	251	72.8
Patient impacted by identification error; nature of impact unknown	78	22.6
Change in patient treatment; no known change in patient outcome	16	4.6

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Clin Chem Lab Med 2016; 54(7): 1141–1145

EFLM Position Paper

Edmée C. van Dongen-Lases, Michael P. Cornes, Kjell Grankvist, Mercedes Ibarz, Gunn B.B. Kristensen, Giuseppe Lippi, Mads Nybo and Ana-Maria Simundic*, on behalf of the Working Group for Preanalytical Phase (WG-PRE), European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

Patient identification and tube labelling – a call for harmonisation

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

PATIENT SAFETY

steps, EFLM WG-PRE recommends the following:

- Healthcare institutions should have zero tolerance to patient identification errors;
- A minimum two and preferably three unique patient identifiers (one of which is the full name of the patient) should be used for patient identification;
- Patient and sample identity should always be checked in the presence of the patient;
- The institution should have a policy and a written standard operating procedure defining the patient and sample identification, which is followed by all personnel;

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HEMOLYSIS

- Practices for *identifying* and *rejecting hemolyzed* specimens are *highly variable* in clinical laboratories.
- Hemolysis is still identified using a *visual scale* by >20% of clinical laboratories in the UK and 48% in the USA.

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Ana Helena Luksic*, Nora Nikolac Gabaj, Marijana Miler, Lora Dukic, Ana Bakliza and Ana-Maria Simundic

Visual assessment of hemolysis affects patient safety

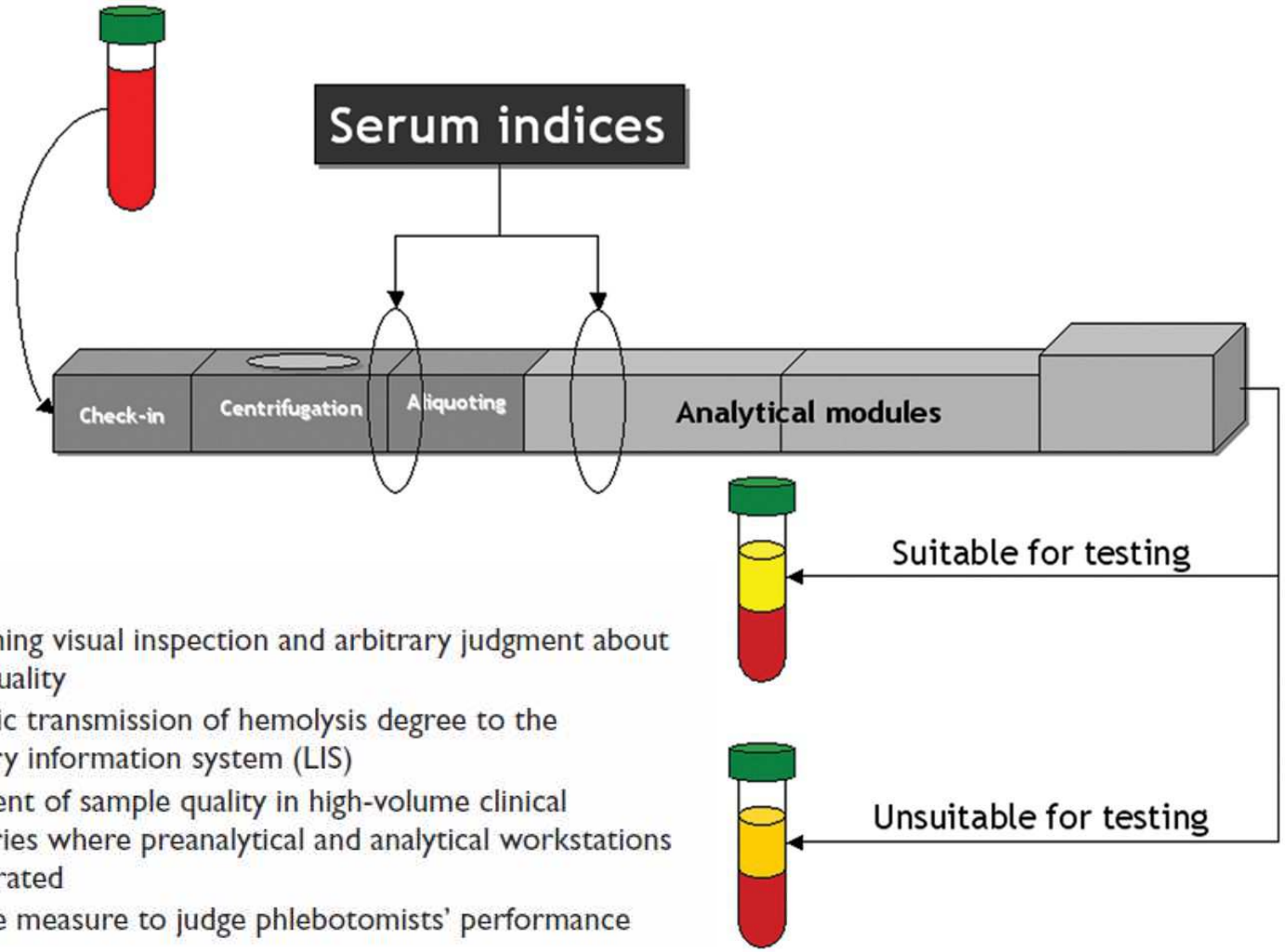
Severity of harm

Occurence probability

	S1	S2	S3	S4	S5 Life-threatening
O5					cTnT
O4	AST, LDH			Bilirubin	K
O3					
O2		ALT	Ca, Cl	CRP, Na, Creat	
O1	ALP, GGT		P, Mg, PROT	Lact, LIP, ALB, CK	Glucose

ISO14971:2012 Medical devices: application of risk management to medical devices.

Visual handling of hemolyzed samples increases the risk of reporting inaccurate results for cTnT, K and bilirubin, possibly affecting the clinical decision and patient outcome.



Advantages

- Overcoming visual inspection and arbitrary judgment about sample quality
- Automatic transmission of hemolysis degree to the laboratory information system (LIS)
- Assessment of sample quality in high-volume clinical laboratories where preanalytical and analytical workstations are integrated
- Surrogate measure to judge phlebotomists' performance

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Giuseppe Lippi & Mario Plebani
Journal of Laboratory Automation 2012;18:184-188

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Clinica Chimica Acta 432 (2014) 38–43

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Clinica Chimica Acta

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

Harmonization of automated hemolysis index assessment and use: Is it possible?

Alberto Dolci [a,*], Mauro Panteghini [a,b]

Clinica Chimica Acta 484 (2018) 328–332

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

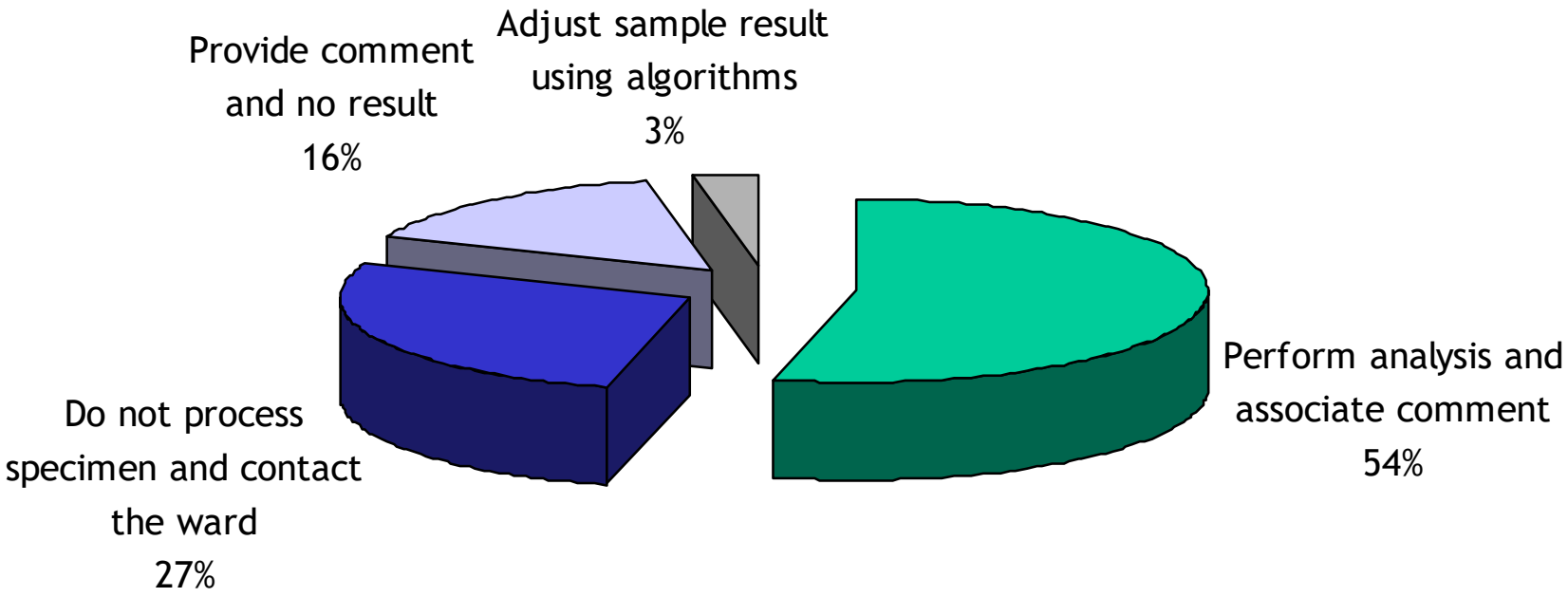
Discussion

Call for more transparency in manufacturers declarations on serum indices: On behalf of the Working Group for Preanalytical Phase (WG-PRE), European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

Alexander von Meyer[a,*], Janne Cadamuro[b], Giuseppe Lippi[c], Ana-Maria Simundic[d]

The availability of interference results reported as continuous values in the LIS is strongly recommended

Harmonize management of unsuitable samples: the most challenging issue?



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Lippi G et al. Clin Chem Lab Med 2006;44:1491

Challenges reported by US primary care physicians when using lab test results

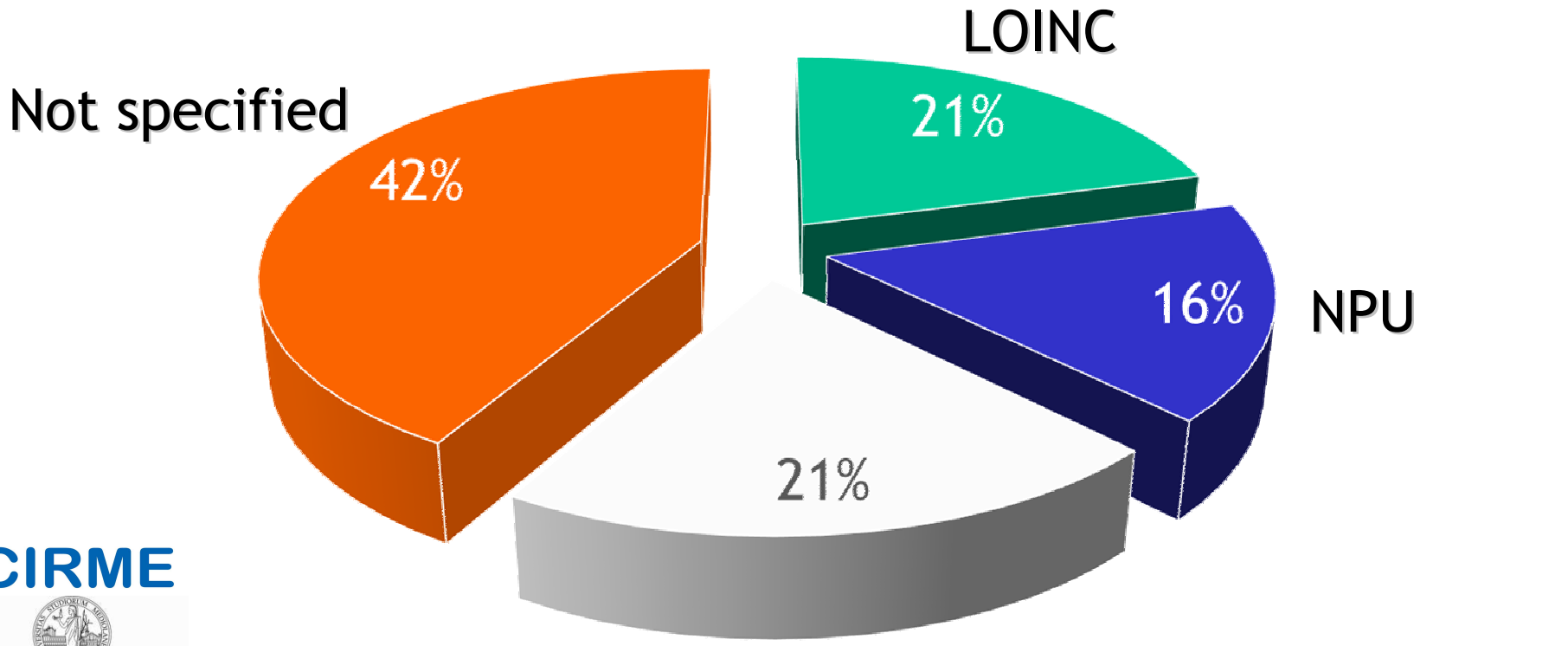
	% of respondents reporting factor is very or extremely problematic
Receiving results	
Results not received in a timely manner	34
Previous results are not easily available	32
Errors in results are suspected	25
Results are inconsistent with patient's symptoms	24
Report format	
Lab-to-lab variation in normal range	22
Lab-to-lab variation in report formats	21
Lab report format is difficult to understand	18
Not enough information in lab report	16

Potentially affecting
13 million pts/yr, raising significant concerns about the safety and efficient use of lab tests

Hickner J et al, J Am Board Fam Med 2014;27:268.

Terminology in Laboratory Medicine: IFCC Survey 2015

Which nationally agreed system of laboratory terminology is in use in your country?



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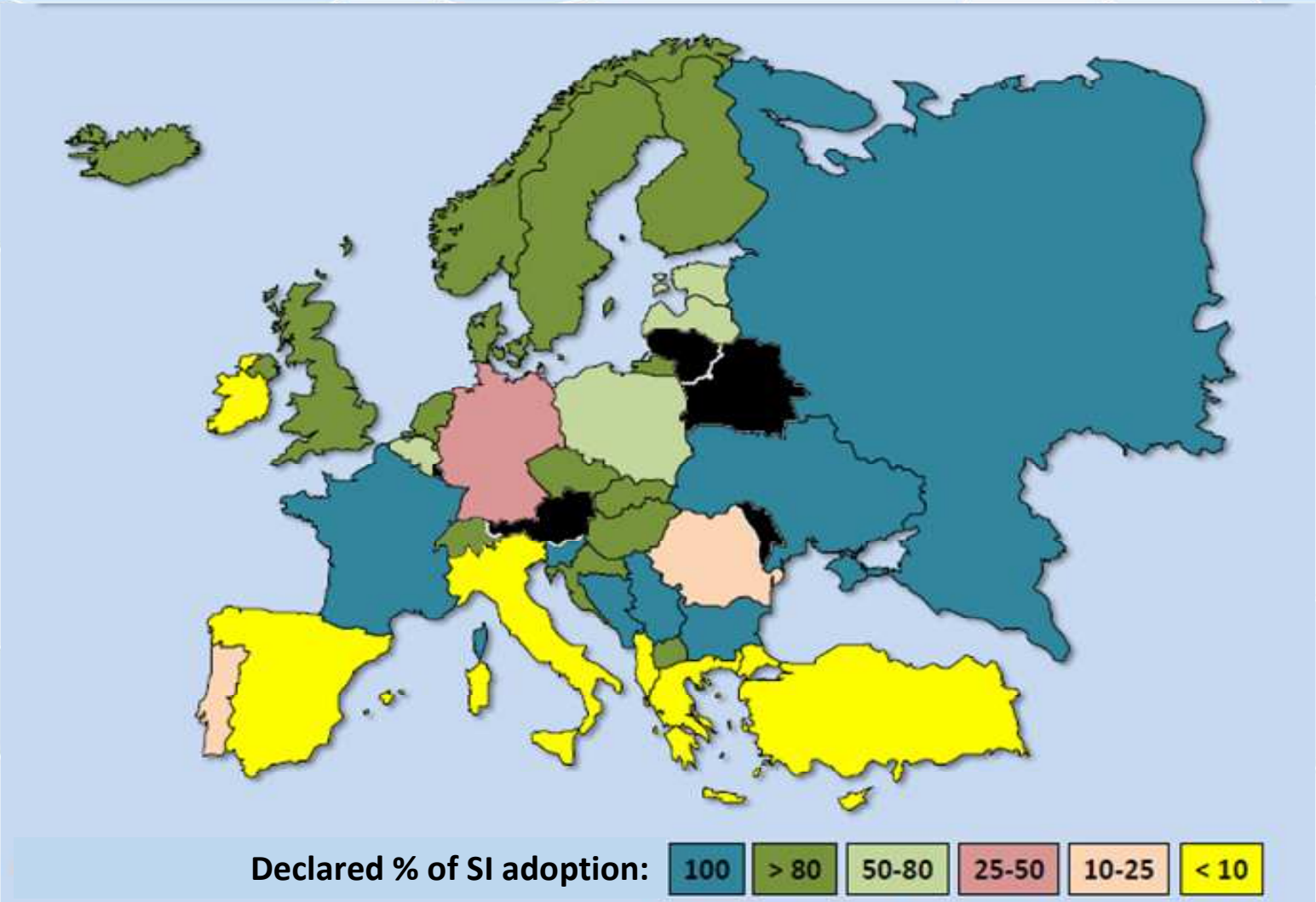
Current use of SI units in Europe



EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Ferruccio Ceriotti*, Najdana Gligorovic Barhanovic, Irena Kostovska, Karel Kotaska and Maria Carmen Perich Alsina, on behalf of the EFLM Working Group on Harmonisation of total testing process

Short report

Decimal numbers and safe interpretation of clinical pathology results

Michael Sinnott,[1,2] Robert Eley,[1,2] Vicki Steinle,[3] Mary Boyde,[4] Leanne Trenning,[1] Goce Dimeski[5]

J Clin Pathol 2014;67:179–181

Take-home messages

- Poor comprehension of decimal numbers was illustrated by many laboratory and clinical staff.
- Resultant misinterpretation of test results is a potential source of medical errors.
- Whenever possible, pathology results should be presented as whole numbers.

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Patient Safety

Barth JH, Panteghini M, Bunk DM et al.
Clinica Chimica Acta 432 (2014) 166

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

Letter to the Editor

Recommendation to harmonize the units for reporting cardiac troponin results

We wish to express a strong recommendation for the reporting in whole numbers and for the use of nanogram per liter (ng/L) as the standard unit for reporting cTns, which is acceptable to the 'Système Internationale' (SI) of Measurement.

Avoiding the unnecessary use of decimals is matter of patient safety… Units for cTn should be harmonized regardless of the analytical sensitivity of the assay used.

Clinical Chemistry 64:4
000–000 (2018)

Editorials

How Clinical Laboratories May Improve Their Performance: The "High-Sensitivity" Troponin Paradigm

Mauro Panteghini[1*]

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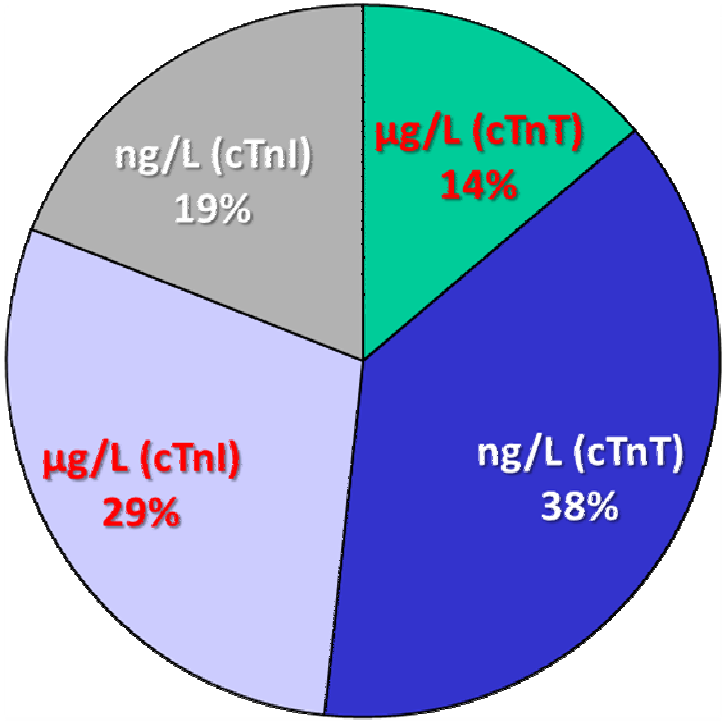
PATIENT SAFETY

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) Study of the EFLM WG Cardiac Markers

Cardiac troponin Units



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Variations in reference intervals: a risk for lab result interpretation

- The used R.I. are often significantly different among laboratories
- The origin of these R.I. may be quite different (manufacturers, literature, internal studies, other laboratories, undefined)
- In the majority of cases, differences among laboratories have no justification

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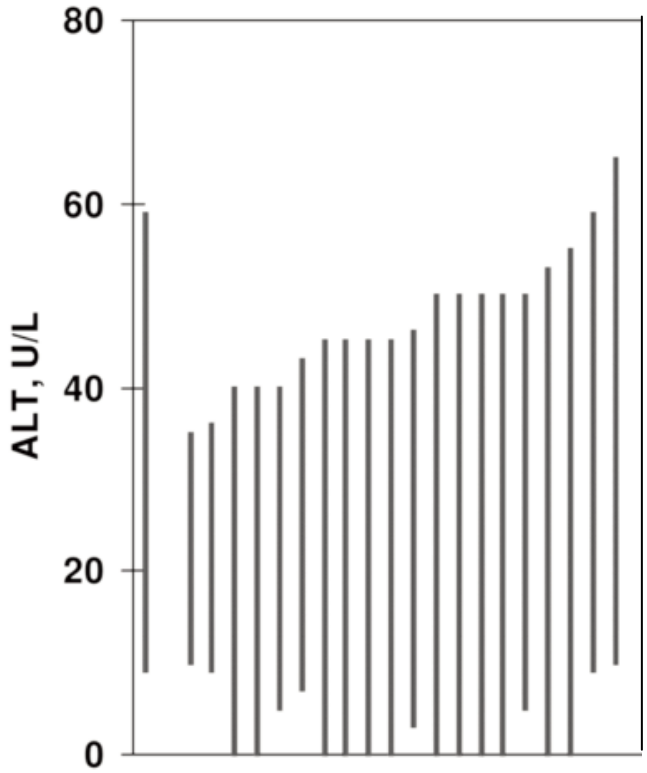
For some analytes, variation in reference intervals is greater than the analytical inaccuracy in their measurement



ALT reference limits (adult male) for same method group: a 2014 national survey

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Cattozzo G. biochimica clinica, 2015, vol. 39, 575.

The ***comparator*** is as important as the ***result***

Clinical Chemistry 63:7
1196–1198 (2017)

Opinion

American Liver Guidelines and Cutoffs for "Normal" ALT: A Potential for Overdiagnosis

Mauro Panteghini,[1*] Khosrow Adeli,[2] Ferruccio Ceriotti,[3] Sverre Sandberg,[4] and Andrea Rita Horvath[5]

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PATIENT SAFETY

Until today

From today

Method-dependent results

Standardised methods that provide traceable results

Method-dependent reference intervals

Traceable reference intervals

Figure 3: Linking the analytical standardisation based on the principles of metrological traceability with the identification of appropriate reference intervals.

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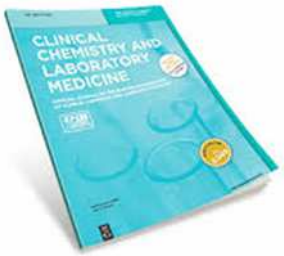


Infusino I, Schumann G, Ceriotti F, Panteghini M. CCLM 2010;48:301
Ferraro S, Braga F, Panteghini M. CCLM 2016;54:523

Common reference intervals for enzymes in adults

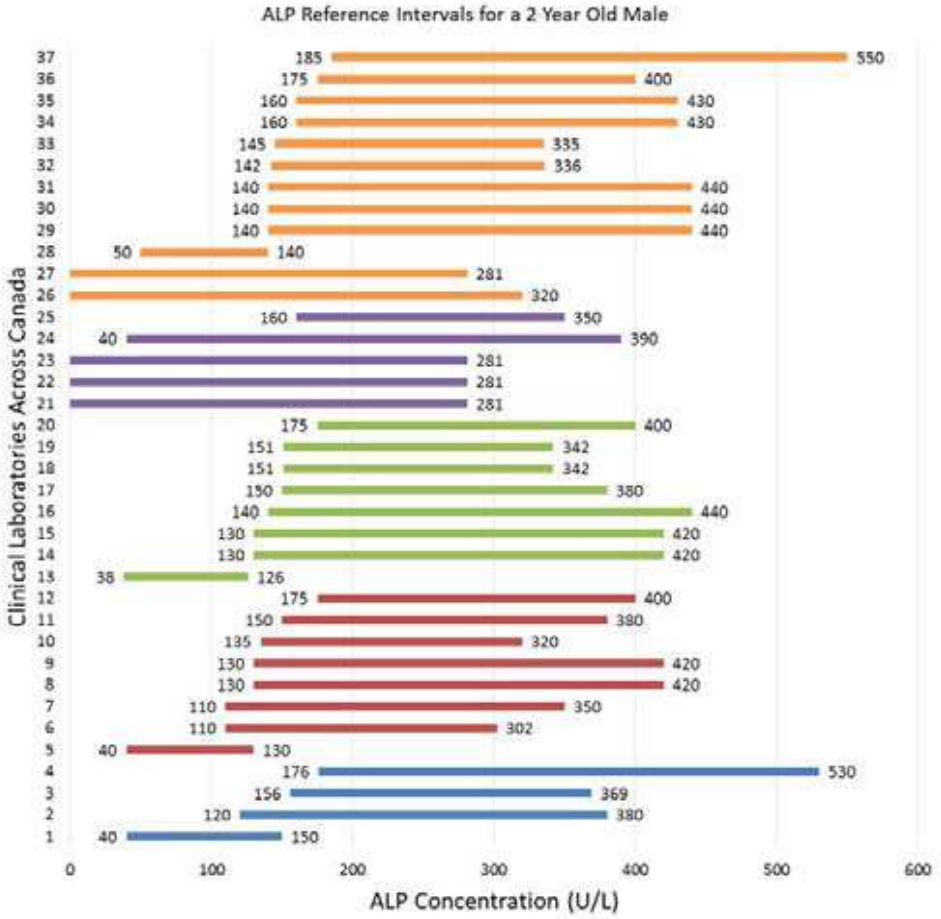
Enzyme	European		Asian	
	Females	Males	Females	Males
AST	11–34		14–32	
ALT	8–41	9–59	11–31	14–54
GGT	6–40	12–68	15–43	15–68
LDH	125–220		138–235	
CK	34–145	46–171	40–152	58–261
AMY	31–107		47–136	
ALP	33–98	43–115	40–106	48–131

Infusino I et al. Clin Chem Lab Med 2017; 55:334-40.

Premise

To be used together with commercial assays that provide traceable results to established IFCC reference measurement systems

ALP pediatric reference intervals: A chaos



Higgins V et al. 69th AACC Annual Scientific Meeting Abstract A-259
Canadian Reference Intervals Survey

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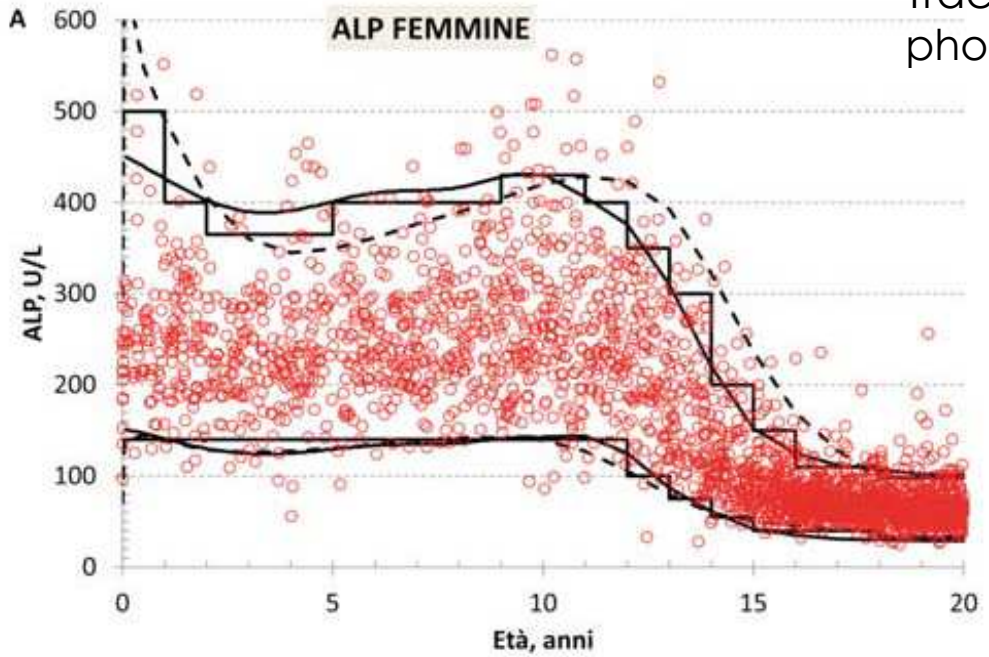
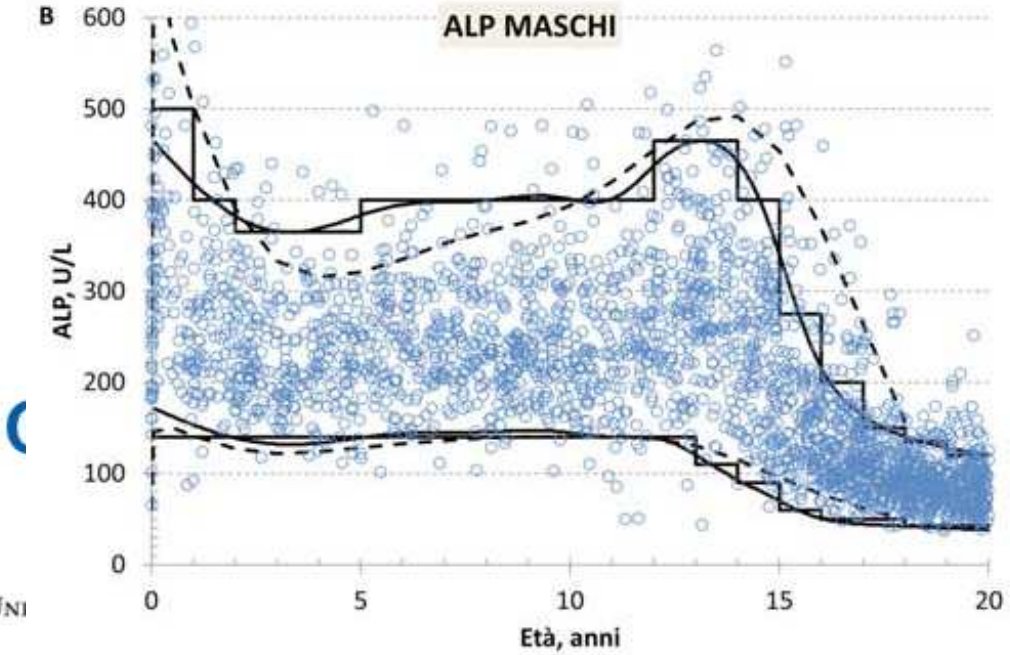
Traceable reference intervals for alkaline phosphatase in serum of pediatrics



Fino a 12 anni: 140 - 400
12-13 anni: 100 - 350
13-14 anni: 75 - 300
14-15 anni: 55 - 200
15-16 anni: 40 - 150
16-18 anni: 40 - 110
19-50 anni: 33 - 98
>50 anni: 53 - 141



Fino a 12 anni: 140 - 400
12-13 anni: 140 - 465
13-14 anni: 110 - 465
14-15 anni: 90 - 400
15-16 anni: 65 - 275
16-17 anni: 50 - 200
17-18 anni: 50 - 150
18-19 anni: 43 - 135
19-20 anni: 43 - 120
>20 anni: 43 - 115

Ceriotti F, Panteghini M, Guerra E et al. Biochimica clinica, 2017, vol. 41, 166

The result standardization issue: an absolute priority for public health

Good results are our contribution to healthcare

→ **Our customers (i.e., doctors and patients) expect laboratory results to be *equivalent for being interpreted in a consistent manner***

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Panteghini M. Clin Chem Lab Med 2012;50:1237

Biased results → Patient harm:

- Wrong diagnosis
- Wrong management
- Incorrect monitoring

The lack of standardization may become an ethical issue

"Standardization of laboratory tests has an ethical dimension as it aims to affect the way diagnostic tests are used in order to guarantee optimal care for patients in a global world."

Bossuyt X et al., Ann Rheum Dis 2008;67:1061

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→ To become *equivalent for being interpreted in a consistent manner*, results must be traceable to higher order references.

EU 98/79/EC-IVD Directive

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on *In Vitro* Diagnostic Medical Devices and repealing Directive 98/79/EC

Official Journal of the European Union

L 117

English edition — Legislation — Volume 60 — 5 May 2017

Contents

I *Legislative acts*

REGULATIONS

* Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1) 1

* Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (2) 176

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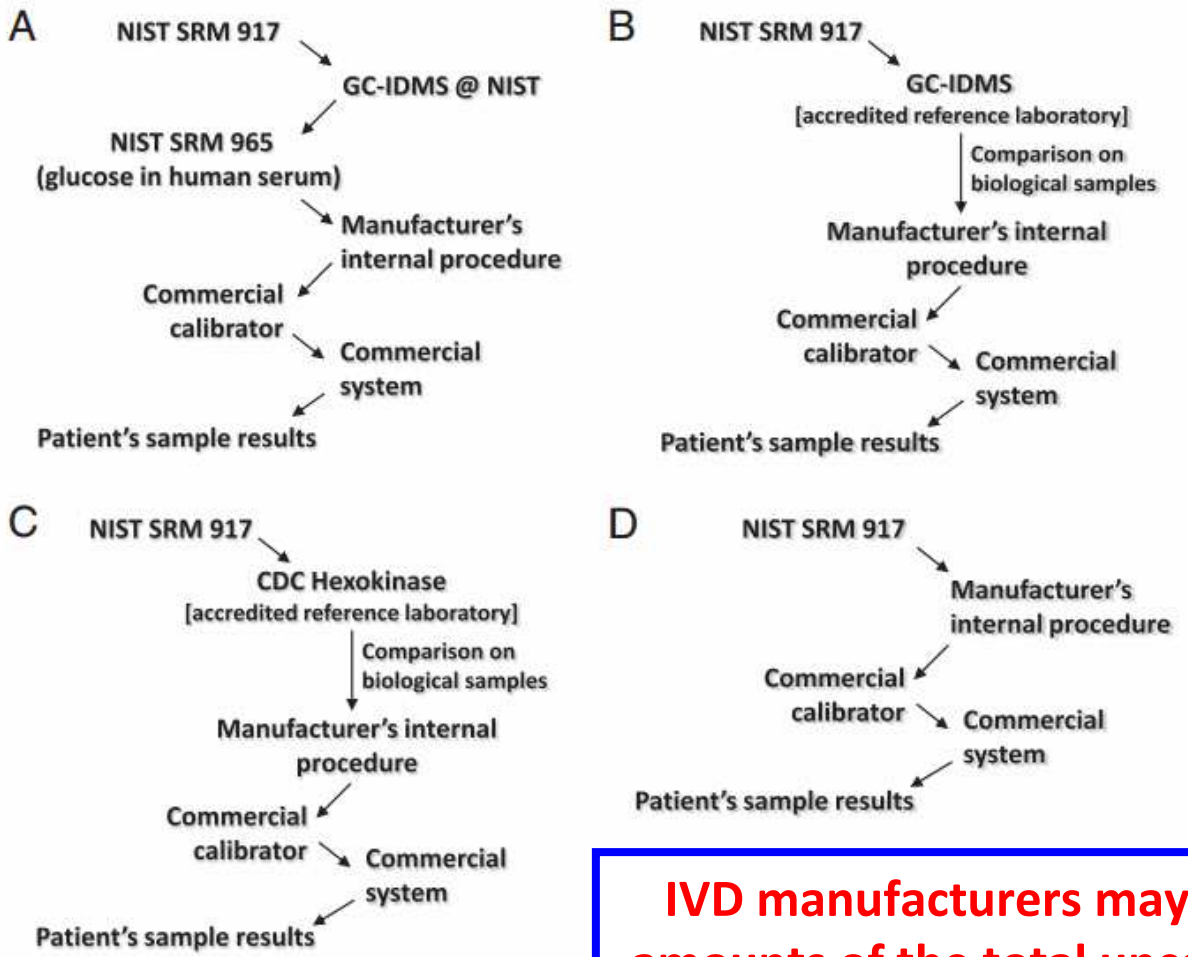
Both require IVD manufacturers to ensure traceability of their measuring systems to recognized higher order references

Role of IVD manufacturers

IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits, which represent a proportion of the uncertainty budget allowed for clinical laboratory results.

[Braga F & Panteghini M, Clin Chim Acta 2014;432:55]

TRACEABILITY CHAINS AVAILABLE FOR IVD MANUFACTURERS FOR PLASMA GLUCOSE



IVD manufacturers may spend different amounts of the total uncertainty budget in implementing traceability of their measuring systems

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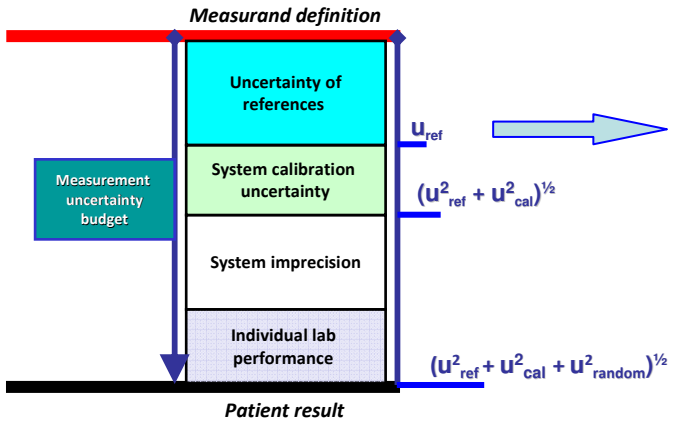
Braga F & Panteghini M. Clin Chim Acta 2014;432:55-61

Braga F, Panteghini M. Clin Chim Acta 2014;432:55-61

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty[a]	Higher-order reference employed		Type of traceability chain used[b]	Combined standard uncertainty associated with the used chain[c]
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22–1.45%[d]
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22–1.45%[d]
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60–3.00%[e]
Roche	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
		GOD	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88–3.26%[f]
		GOD	Chemistry calibrator	0.80%	Hexokinase	NIST SRM 917a	C	1.88–3.26%[f]



Chain A = 0.73% vs. Chain C = 1.63%

4.05% minimum

2.70% desirable

1.35% optimum

The quality of glucose measurement may be dependent on the type of traceability chain selected for trueness transferring, sometimes making difficult (e.g., chain C) to achieve the suitable limits for measurement uncertainty on clinical samples

The Essential Question…

“What amount of medical harm due to analytical error is it ok to let go undetected?”

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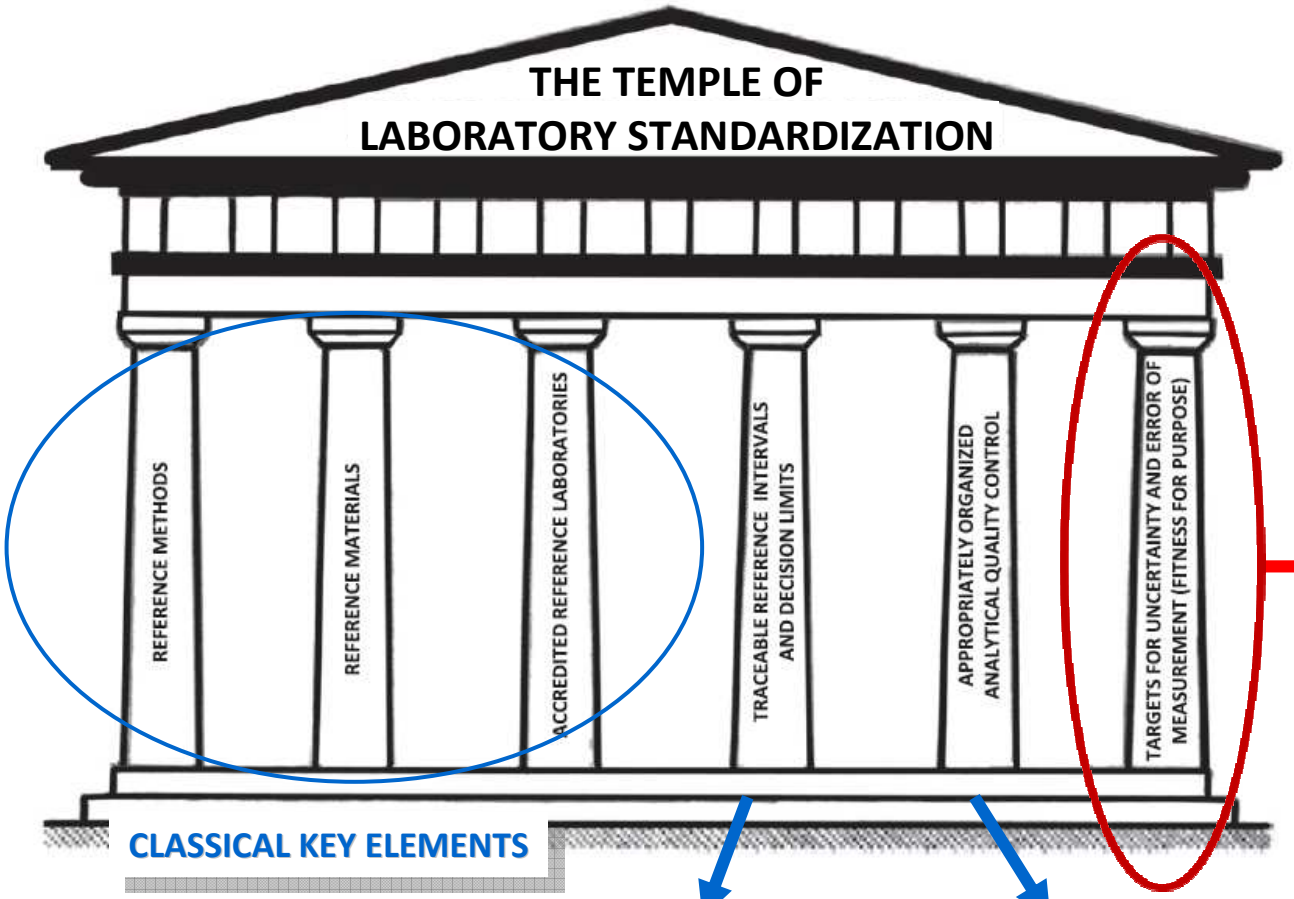
Patient Safety

THE TEMPLE OF LABORATORY STANDARDIZATION



CLASSICAL KEY ELEMENTS

6th pillar
TARGETS FOR UNCERTAINTY AND MEASUREMENT ERROR THAT FIT FOR PURPOSE

4th pillar
TRACEABLE REFERENCE INTERVALS AND DECISION LIMITS

5th pillar
ANALYTICAL (INTERNAL AND EXTERNAL) QUALITY CONTROL THAT MEETS METROLOGICAL CRITERIA

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Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

EFLM Paper

Mauro Panteghini*, Ferruccio Ceriotti, Graham Jones, Wytze Oosterhuis, Mario Plebani and Sverre Sandberg, on behalf of the Task Force on Performance Specifications in Laboratory Medicine of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

Strategies to define performance specifications in laboratory medicine: 3 years on from the Milan Strategic Conference

Model 1: Based on the effect of analytical performance on clinical outcomes a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes; b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.
Model 2: Based on components of biological variation of the measurand.
Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).

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EFLM

Accred Qual Assur (2008) 13:145–148
DOI 10.1007/s00769-008-0364-z

Marjan Van Blerk et al.

There are as many limits as there are EQA providers

GENERAL PAPER

Comparison of evaluation procedures used by European external quality assessment scheme organizers for haemoglobin concentration and leukocyte concentration

Table 1 Criteria used for acceptable performance for haemoglobin concentration in blood and leukocyte concentration (deviation from the target value)

Scheme	Haemoglobin concentration	Leukocyte concentration
Belgium	±2*s*	±2*s*
France	±2*s*	±2*s*
Spain (two organizers)	±2*s*	±2*s*
Croatia	±1*s*	±1*s*
Germany	±6%	±18%
Finland	±5%	±10%
Hungary: consensus mean	±3%	±6%
Hungary: target value set by reference labs or manufacturers	±5%	±15%
Russia	±1.64*s*	±1.64*s*
Slovenia	±4%	±10%
Switzerland: QUALAB (official for licensing)	±9%	±25%
Switzerland: CSCQ (scientific approach)	±3%	±8%
New York State, USA	±7%	±15%

Table 2 Percentages of unsatisfactory results reported by the participating EQAS organizers for a fixed set of 262 results of haemoglobin concentration in blood and leukocyte concentration

Scheme	Haemoglobin concentration	Leukocyte concentration
Belgium	6.9	7.3
Croatia	14.9	15.3
Finland	1.5	3.1
France	5.4	4.6
Hungary: consensus mean method	13.5	19.8
Russia	15.6	19.8
Spain 1	7.6	4.6
Spain 2	3.1	2.3
Switzerland: QUALAB (official for licensing)	0.4	0
Switzerland: CSCQ (scientific approach)	0.8	2.0
New York State, USA	0.8	2.3

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Graham R.D. Jones*, Stephanie Albarede, Dagmar Kesseler, Finlay MacKenzie, Joy Mammen, Morten Pedersen, Anne Stavelin, Marc Thelen, Annette Thomas, Patrick J. Twomey, Emma Ventura and Mauro Panteghini, for the EFLM Task Finish Group – Analytical Performance Specifications for EQAS (TFG-APSEQA)

Analytical performance specifications for external quality assessment – definitions and descriptions

Basic elements that need to be considered:

a)nature of the EQA material, including commutability, which may affect the result interpretation;

b)procedure used to assign the target value;

c)data set to which APS are applied;

d)analytical property being assessed (i.e., TE, bias, imprecision);

e)rationale for the selection of the APS;

f)type(s) of model used to set APS

We need these to:

1.compare APS from EQAs

2.inform users about the APS they use

3.plan standardization (common EQA APS would support uniform analytical performance and true quality improvement)

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Analytical performance specification (APS) derivation should be added to the Miller's EQAS categorization

[Miller WG et al. Clin Chem 2011;57:1670]

				Evaluation capability				
				Accuracy				
				Individual laboratory				
	Sample characteristics				Relative to participant results		Reproducibility	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV
1	Yes	Yes	Yes	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X

Category 1/2A → Milan model 1 or 2 as basis for APS
Category 1/2B → Other models

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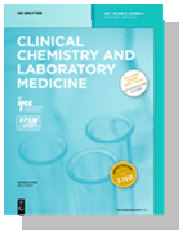
Infusino I et al. Clin Chem Lab Med 2017;55:334



Evaluation of Standardization of Cystatin C Measurement

Validated commutability

EQA
Category 1A

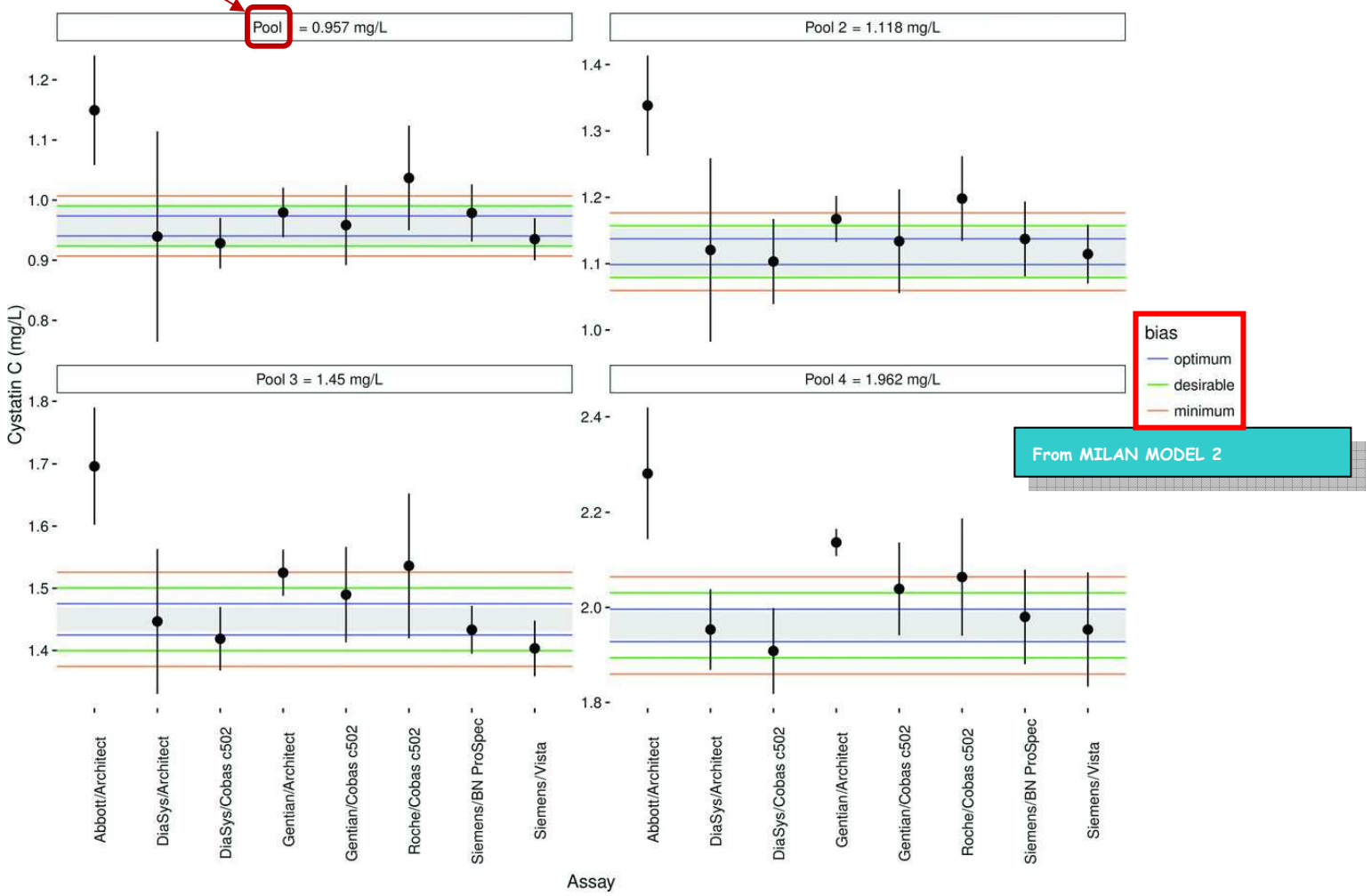


Fig. 1. Biases between the commercial assays and the IDMS target value for CysC.
The figure shows the reference material values and the areas of their uncertainty (gray zone), the mean (SD) of the results from the evaluated systems, and lines depicting the bias specifications (red, green, and blue lines correspond to the optimal, desirable, and minimum quality levels, respectively).

Bargnoux AS et al. Clin Chem 2017;63:833

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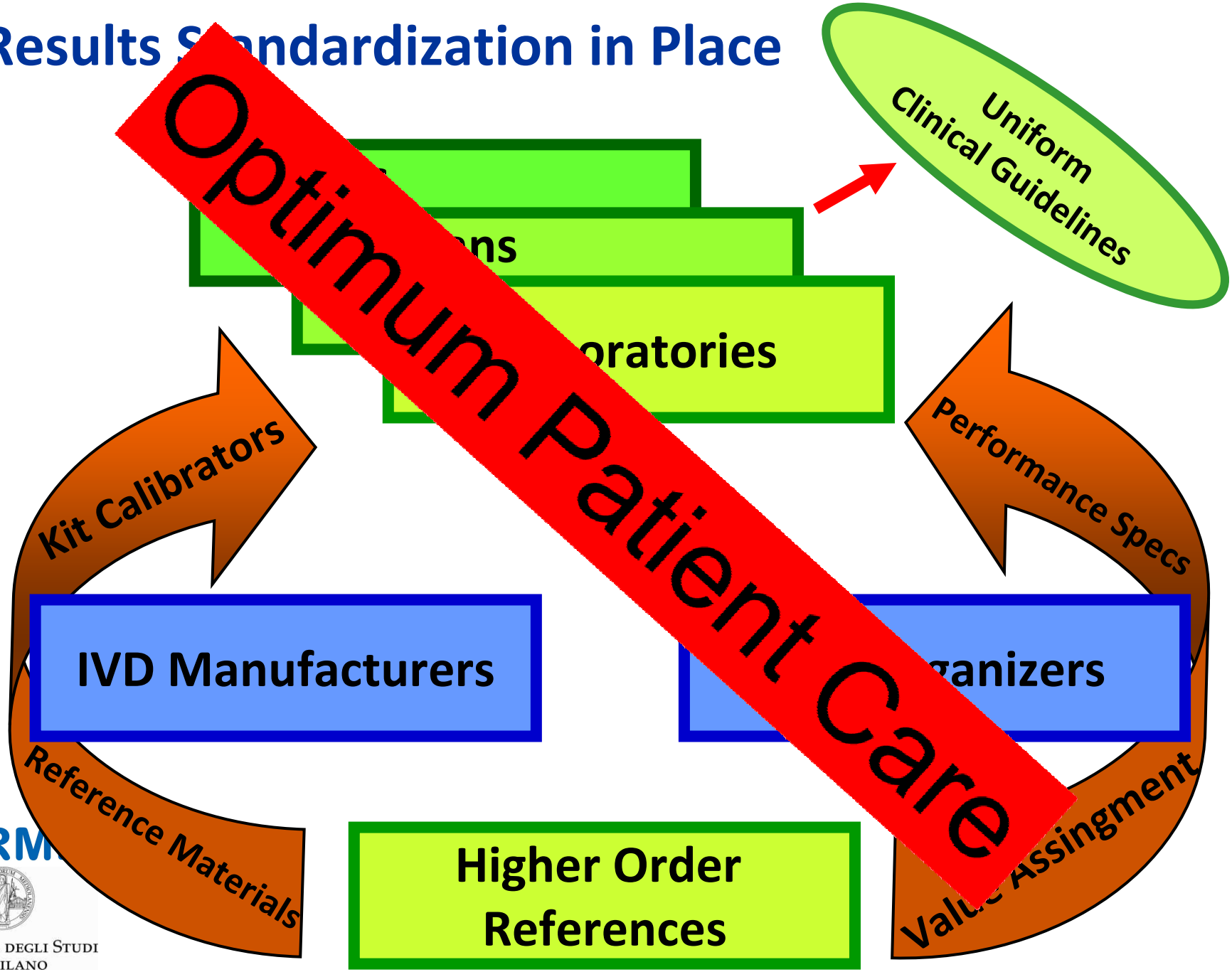
Results Standardization in Place



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Key Messages

- As leaders in our profession we have a key role to play in facilitating better patient's outcome
- One barrier to improved outcome is excessive variability
- Only a relatively small percentage of procedures within the total examination process (TEP) have been standardized or harmonized
- Where TEP procedures have been standardized evidence of improved clinical outcome is emerging
- As a profession we should:
  - Facilitate the standardization of many procedures as possible
  - Work with clinical colleagues to demonstrate improved outcomes

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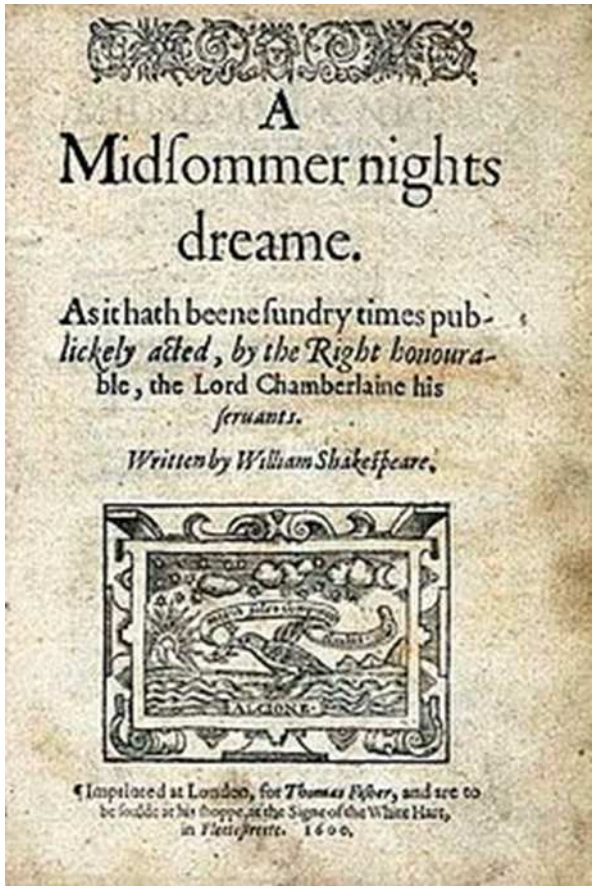
A
Midſommer nights
dreame.
As it hath beene ſundry times pub-
lickely acted, by the Right honoura-
ble, the Lord Chamberlaine his
ſeruants.
Written by William Shakeſpeare.
¶ Imprinted at London, for Thomas Fiſher, and are to
be ſolde at his ſhoppe, at the Signe of the White Hart,
in Fleetſtreete. 1600.

Thus, we should pursue standardization as Shakespeare urged for truth:

"…till truth makes all things plain."

[A Midsummer Night's Dream, Act V, sc. 1]

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